1) Title

Development of a Duchenne Muscular Dystrophy Registry in South Africa to optimise care

By

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6) Abbreviations

ACE	Angiotensin converting enzyme
BMD	Beckers Muscular Dystrophy
CK	Creatinine Kinase
CNS	Central Nervous System
CRC	Clinical Research Council
DCM	Dilated cardiomyopathy
DMD	Duchenne Muscular Dystrophy
ECG	Electrocardiogram
ERG	Electroretinogram
FSIQ	Full Scale Intelligence Quotient
FVC	Forced Vital Capacity
ID	Intellectual Disability
IMD	Intermediate type Muscular Dystrophy
LOVD	Leiden Open Variation Database
LSDB	Locus Specific Data Base
NMD	Neuromuscular Disease
PANDA	Paediatric Neurology and Development Association of South Africa
PEG	Percutaneous endoscopic gastrostomy
QOL	Quality of life
REDCap	Research Electronic Data Capture
RCWMCH	Red Cross War Memorial Children's Hospital
SADMD	South African Duchenne muscular dystrophy registry
TREAT-NMD	Neuromuscular registry in Europe
UMD- DMD	Utrophin muscular Dystrophy DMD
XLDMC	X-Linked Dilated Cardiomyopathy

7) Abstract

Background
The most prevalent, most lethal of the inherited dystrophies is Duchenne Muscular Dystrophy (DMD) and globally, the incidence is 1 in 3500 live male births. Currently, DMD has no cure, the latest care guidelines, especially on corticosteroids, cardiac interventions, and non-invasive ventilation, are all associated with improved muscle function, survival and quality of life. This reflects the fact that the natural history of DMD has been changed by these effective measures. Despite these advances, the progression and disastrous outcome of the disease cannot be modified and DMD remains life limiting. Potential therapeutic approaches that target the causative genetic variations raise hopes of promising treatment for DMD. Many clinical trials of molecular genetic therapies have been planned and conducted for DMD. In South Africa, even though mutational characteristics of South African DMD/BMD patients have been described in several studies, the development of experimental therapies faces many challenges due to the lack of epidemiological data, the natural history of the disease and information about clinical care amongst Africans. Understanding the disease course of the local population can lead to better care approaches, further with the possibility of gene therapy becoming available, patients that would qualify for such treatment need to be identified. Hence the need for a DMD specific disease registry
Objective: This study aim to describe the concept and design of the first DMD disease registry of South Africa using Research Electronic Data Capture (REDCap)

Methods: A comprehensive literature review was undertaken to identify the key areas of DMD, which must be recorded to permit comparison across disease expression and intervention variables. The registry was developed using REDCap's web based online designer accessed through the Clinical Research Centre (CRC) in the Faculty of Health Sciences at the University of Cape Town, and the workflow methodology was adopted to manage the registry. Clinical data from DMD patients form the database and consists of seven parts: 1) Enrolment details, 2) Background data, 3) Current disease, 4) Schooling, career prospects, and life style/psychological details, 5) basic activity of living scale, 6) power chart,7) current motor function/symptoms. Electronic case report forms were created from these clinical data by the use of REDCap and for specific variables serial entries were possible relating to disease progression. We adopted international data standards proposed by TREAT-NMD, a global network of registries on DMD to ensure our data is internationalised and comparable to other registries.

Results: Retrospective data entry combined with dynamic prospective recording of data was utilized in this project. Building on an existing basic database, 100 confirmed DMD boys are currently eligible for inclusion into the registry.
The registry database consist of 7 forms collecting information on clinical and genetic information, which is subdivided into 100 items making a total of 210 variables. As our registry is an on-going study, sequential analysis of accumulated data will done going forward to review trends on our DMD patients.

Conclusions: This work describes the concept and design of our DMD registry and the steps followed to its establishment with REDCap. The focus is to consolidate clinical and genetic information on South African DMD patients that will translate to clinical research and form the basis for this patient information to be linked nationally and internationally. It is the hope that such an effort can be replicated in the conceptualisation of new disease registries

8) Chapter 1: INTRODUCTION AND LITERATURE REVIEW

8.1 Introduction

The most frequent form of muscle dystrophy found in childhood is Duchenne Muscular Dystrophy (DMD) and it is the most severe in the spectrum of muscle diseases termed the dystrophinopathies. The natural (untreated) history of DMD comprises: delayed milestones (sitting, standing), mean age of walking 18 months, mean age of diagnosis 5 years, proximal skeletal muscle weakness and waddling gait with difficulty climbing stairs, and wheelchair bound by 12 years. A milder form in the spectrum of dystrophinopathies is Becker muscular dystrophy (BMD), with delayed skeletal muscle weakness of later-onset, and preserved neck flexor muscle strength (unlike DMD), and patients remaining ambulatory until beyond 20 years of age. Wheelchair dependency occurs in DMD before 13 years, whereas it occurs in BMD after 16 years; this differentiates the two. There is a third clinically important dystrophinopathy, where cardiac muscle is predominantly affected and it is called DMD-associated dilated cardiomyopathy (DCM). This is a distinct entity where, reportedly, males present between 20 and 40 with cardiac failure, although we have seen at least one patient presenting in our service with heart failure at the age of 14 years; DCM can also be seen in at risk female carriers of DMD mutations.

The primary problem is a mutation in the dystrophin gene located on chromosome X (Xp21.2) and the inheritance is via X-linked recessive fashion.

Gene therapy is a technique, which involves treating a genetic disease by altering the defective gene. The possibility of gene therapy and experimental genetically driven interventions in DMD has been investigated for some time and great progress has been made. A crucial aspect of the treatment is that the genetic defect needs to be characterized.

Since January 2007, TREAT-NMD, through collaboration has enabled experts to come together and to establish common standards of care, bringing together the neuromuscular community to speed up clinical trials and increase awareness of rare diseases such as Duchenne Muscular Dystrophy.

The dedicated neuromuscular service at Red Cross War Memorial Children's Hospital manages the single largest collection of boys with DMD in sub-Saharan Africa. The service operates in line with international recommendations as a multidisciplinary service with input from ancillary services, pulmonology, cardiology, developmental, orthopaedics, endocrinology, histopathology, genetics and counsellors. With the possibility of treatment becoming available, patients that would qualify for treatment need to be identified. The service has established a database of these children with confirmed DMD, but there is a need to consolidate the information in the database to form a patient registry.

DMD is a rare disease, and therefore, it will take many years to find eligible patients for trial without a registry. The South African DMD (SADMD) registry is the first local attempt to consolidate clinical and genetic information on South African DMD patients with the potential to be considered for contemporary clinical trials and be well informed regarding the most up to date standards of care. This cohort will provide the biggest longitudinal data collection of DMD boys in Africa with the possibility of links with programs of excellence such as TREAT-NMD.

8.2 Objectives

The cardinal objectives of the SADMD registry are, to update and expand the existing database.

- To populate it with current information relating to the clinical phenotypes of the patients inclusive of their cardiac, respiratory, cognitive, oromotor / gastroenterological, motor and orthopaedic evolution.

- To assess the effect of introduction of corticosteroids and cardiac interventions on the course of these children for their cardiac and pulmonary, duration of ambulation, orthopaedic complications and resultant need for BIPAP support.

- To correlate the clinical profile of this patient group with those who have confirmed genetic mutations and identify those who may be remedial for the latest gene therapy and who would benefit from extended screening to confirm if this is the case.

- To establish if the South African cohort carry a similar range of mutations compared to those listed internationally

- To see if direct relationship can be identified between specific mutation and clinical course

- To identify if the range of patients carrying potentially remedial gene therapy mutations is in-line with the incidence reported internationally

8.3 Search Strategy

The literature review, which was done in May 2015 and repeated in February 2017, Was done using mostly Ebscohost, Pubmed, and Web of Science. The search terms included key words: [Rare disease] [Rare disease registry] [Disease registries] [Duchenne muscular Dystrophy] [Treat NMD][REDCap]. Bibliographic references of important articles were also manually searched for added publications.
Articles were included if they studied rare disease registries, registry design and concepts, and all in the English language.

8.4 Search Results

In total, 50 articles resulted from the search above, of which 42 full articles were were reviewed and 35 included in the literature review. At the same time, a further 48 articles were found and added from the Bibliographic reference list.

8.5 Background Information

Dystrophinopathy is the umbrella term for a group of inherited progressive muscle disorders due to mutation in the dystrophin gene on the X-chromosome (Xp21.2) and required for a normal muscle function (1) (2, 3). Mutation in this gene results in no or abnormal dystrophin in muscles and this manifest as muscle weakness (1, 3).

The identification of the dystrophin gene in the 1980's, led to the characterization of a number of muscular dystrophy genes and their protein products. The information on the molecular basis of muscular dystrophies resulted in better understanding of the disease mechanisms and improved diagnosis, both in the clinic and in the laboratory. This

knowledge has led to the availability of more reliable and informative genetic testing, which allows for more effective patient management and accurate genetic counseling of families (4).

The allelic Duchenne and Becker muscular dystrophies (D/BMD) remain lethal and devastating to patients and their families, despite recent advances in medical technology (3). While standards of care are continually improving worldwide, currently available interventions are limited to the management of symptoms and complications. Progress in terms of therapy has been slow and fraught with pitfalls and setbacks. However, much research has been focused on genetic therapies, and in recent years a number of new experimental approaches appear to hold promise. Of those, read-through therapy and exon skipping are especially relevant to D/BMD (3, 5, 6).

Nonetheless, the first step remains identification of the disease-causing mutations. Potential availability of mutation-specific gene therapy marks the advent of personalised medicine and emphasizes the need for a rapid and accurate method of detecting small nucleic acid changes in D/BMD and other genetic disorders.

MUSCULAR DYSTROPHIES

Neuromuscular diseases are a well-defined spectrum of heterogeneous, hereditary disorders, characterised by on-going weakness and wasting of skeletal muscle tissues (3, 7). Muscular dystrophies form part of this spectrum. The main groups in the spectrum are:

- Duchenne/Becker-type (X-linked)
- Facioscapulohumeral (autosomal dominant)
- Limb girdle (genetically heterogeneous but mostly autosomal recessive)
- Emery-Dreifuss (X-linked, autosomal dominant and recessive sub-types)
- Distal (autosomal dominant and recessive clinically and genetically distinct subgroups)
- Oculopharyngeal (autosomal dominant)
- Congenital (autosomal recessive with a more generalised muscle weakness)

This Classification scheme devised by Walton and Nattrass in 1954, based on their own clinical observations and still applied today, relies mostly on the distribution of muscle weakness (Figure1), and the mode of inheritance (3, 7)

Muscular dystrophies have since been mapped to 29 different chromosomal loci, shifting the above classification into 34 different disorders with difference in the age of first symptoms, degree of severity, pattern of inheritance and the predominantly affected muscle groups (3, 8).

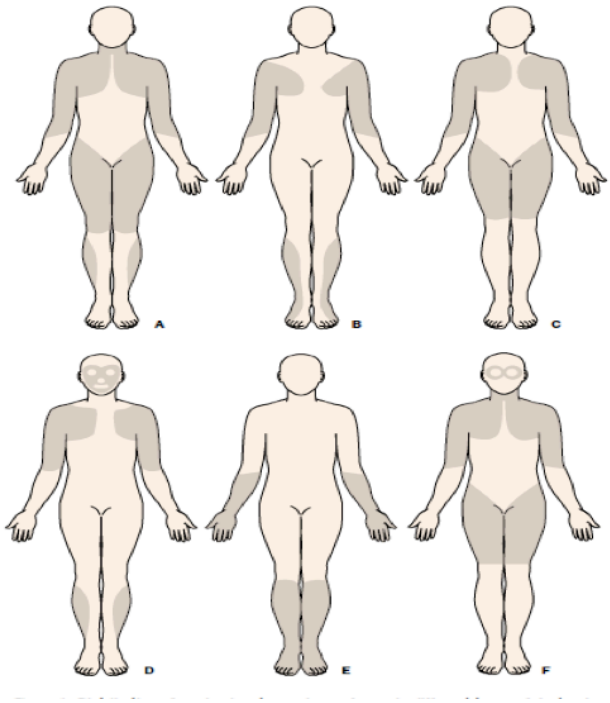

Figure 1: Different types of Muscle dystrophy with typical distribution of predominant muscle weakness:
A: *Duchenne-type and Becker-type, B: Emery-Dreifuss, C: limb-girdle, D: facioscapulohumeral, E: distal, F: oculopharyngeal. Shaded=affected areas (3). (1, 9, 10) Reproduced with permission from Alan E H Emery, muscular dystrophies, BMJ, Oct 10.1998, vol 317, Liscense number* 4106711480102(see appendix 6)

GENETICS OF DUCHENNE/BECKER MUSCULAR DYSTROPHY (D/BMD)
(OMIM#310200)
Duchenne Muscular Dystrophy is a genetic disorder with an X-linked recessive inheritance (10, 11). This disorder results from mutations (often deletions) in the dystrophin gene on the X chromosome (Xp21.2) (1, 10, 12). It has a frequency of 1 in 3600– 6000 male births (1, 2, 13). The DMD gene is the largest known human gene. It is around 2000 kilobases in size and codes for dystrophin, a large, rod-like 427-kD protein containing 3685 amino acids and located at the inner face of the muscle cell membrane (14-16). Dystrophin interacts with a group of 'dystrophin-associated proteins' (DAPs) (e.g. sarcoglycans, dystroglycans, merosin) that span the muscle membrane, linking the cytoskeleton of the muscle and the extracellular matrix (see Figure 2.0). Absence of dystrophin disrupts the link, making the membrane of muscles susceptible to damage from shearing forces. Hence, muscles deficient in dystrophin are liable to injury, and degeneration of muscle fibres is a feature of dystrophic muscle (10).

Dystrophin is undetectable in the muscle of DMD patients. With access to MLPA, 70% of all DMD mutations are identifiable in males with DMD, making genetic testing highly sensitive in clinical settings (17, 18). Over 4700 mutations in the DMD gene have been identified. Disease-causing alleles varied and can be complete, involving the entire deletion of a gene, exon deletion/duplication, insertions, as well as deletions that are small and replacement of a single base (2, 10, 19). Around two thirds of DMD patients have intragenic out-of-frame deletions with gross rearrangement, duplications of more than one exon of the gene are found in about 10% of patients, the rest have small rearrangements including insertions of repetitive sequences, intronic deletions, and splice site mutations as well as point mutations (2, 10, 20, 21).
Generally out-of-frame mutations cause lack of dystrophin (and DMD), whereas in-frame mutations cause abnormal but partially functional dystrophin, resulting in BMD (2, 21, 22). The tissue distribution of dystrophin correlates with clinical features. It is found in skeletal, cardiac and smooth muscle, and results in skeletal muscle weakness and cardiomyopathy. Abnormal expression of myocardial dystrophin is noted in DMD-associated DCM, mildly reduced amount of dystrophin in skeletal muscle DMD (23, 24). Dystrophin is found within the central nervous system, resulting in a static encephalopathy and cognitive deficits. Various forms of dystrophin are expressed in neurons and glia in the brain, especially the cortex, hippocampus, cerebellum and retina (25). Confirmed diagnosis of DMD can be made with molecular genetic testing in around 70% of patients with no need for muscle biopsy in these patients. New mutations are now showing peak incidence and over 60% of all new mutation have no significant family history (24, 26).

GENETIC MUTATIONS AND DYSTROPHIN

Mutations

Predominantly, one or more exon deletions constitute dystrophin gene mutations, which are found largely in patients with DMD and BMD, (2, 9, 27-29). Reported in small proportions of affected individuals are a small percentage of partial gene duplications (30) (31)

The genetic lesions in the remaining patients (ie, without detectable deletions or duplications) are single nucleotide variants, small deletions or insertions in the coding sequence, or splice site variants. In addition, patients with clinical phenotypes consistent with DMD or BMD, but not with an apparent X-linked pattern of inheritance, may have defects in other genes, including those encoding the dystrophin-associated glycoproteins as depicted in figure 2(3, 32).

The molecular basis for the phenotypic differences among the dystrophinopathies is related in part to whether the reading frame for dystrophin is preserved. Disruption of the reading frame for dystrophin is the lesion in most cases of patients with DMD while those with BMD have mutations that maintain the amino acid coding sequence (32)

Dystrophin — (figure 2) (33-35). Mechanically, it lends support and protection to the sarcolemma and the glycoprotein complex, preventing it from degradation. When dystrophin is absent, the glycoprotein complex is exposed to proteases and eventually

digested. This process initiates the degeneration of muscle fibres, leading to muscle weakness.

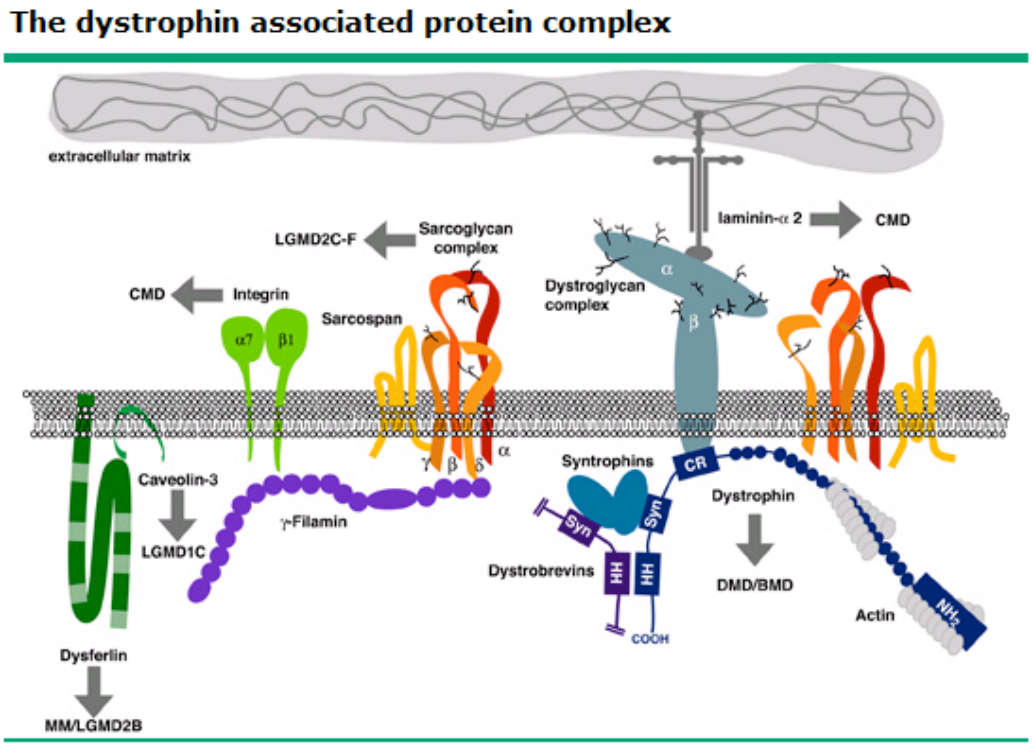

Figure 2: **Dystrohin associated protein complex,** *Reproduced with permission from Alan E H Emery, muscular dystrophies, BMJ, Oct 10.1998, vol 317, Liscense number* 4106711480102(see appendix 6)

The loss of dystrophin in mdx mice leads to myofibril membrane instability (36). However, the dystrophin gene disruption in mdx mice resulted in only a mild dystrophy (37). Although the reduced disease severity in mdx mice compared with human DMD is not completely understood, several possible explanations are postulated as follows:

I. A homolog of dystrophin called utrophin is present in mice and humans. Its expression in muscle can compensate physiologically for the absence of dystrophin in mice, but this compensation does not occur in humans. This hypothesis underpines the finding that, mice lacking both dystrophin and utrophin have severe dystrophy, which phenotypically resembles DMD (37).

Further, the selective expression in skeletal muscle of utrophin via the use of a transgene completely rescues these double-knockout mice from early death and the DMD phenotype (8).

II. For sialic acid N-glycolylneuraminic acid (Neu5Gc) to be expressed in humans, cytidine monophosphate-sialic acid hydroxylase gene (CMAH) is required (38). However, CMAH is documented as absent in humans because of an inactivating deletion. But, most mammals, including mice, can express Neu5Gc and incorporate it onto glycolipids and glycoproteins in skeletal and cardiac muscle, a factor that may ameliorate disease expression in mdx mice (29). In support of this theory, disease severity is accelerated and more closely resembles human DMD if mdx mice also carry mutation in the Cmah gene that looks like the one found in humans (29).

III. Compared with the murine type, human muscle stem cells have shorter telomeres, which result in progressive loss of muscle stem cell function. The severity of human DMD may be due in part to the loss of useful muscle stem cells, making it impossible to repair the momentous muscle injury that occurs as part of this disease (39). In support of this hypothesis, "double knockout mice (mdx/mTR) have shortened telomeres in muscle cells and develop a severe muscular dystrophy" similar to human DMD (3, 40).

In the the glycoprotein complex of the sarcolema, dystrophin has a number of associated proteins, one of which is known as neuronal nitric oxide synthase (nNOS) (41). This sarcolemmal synthase enzyme is important for nitric oxide formation, and mediates vasodilation leading to increased blood flow into muscles, preventing of early muscle fatigue with activity (42-44). Loss dystrophin is equal to a loss of muscle nNOS in their manifestation (41, 45), leading to early muscle fatigue with activity (42-44, 46).

Calcium disregulation may sometimes have a role in the disease process of DMD (47-50). Loss of dystrophin, causing muscle cell membrane damage, may permit extracellular calcium into muscle fibers. Besides, mediators of inflammation in dystrophic muscle tend to induce nitric oxide synthase (iNOS) expression, making it bind and destabilizes sarcoplasmic ryanodine receptors to regulate the flow of calcium ion (51-53). As a result, calcium leaks from the sarcoplasmic reticulum to reach the cytosol. The accumulated cytosolic calcium has the ability to promote muscle proteolysis by activating calpains (53, 54).

Other genetic modifiers — accumulating data suggest that genes other than dystrophin affect disease severity and response to treatment (55-57). As an example, a variant of the SPP1 gene promoter region (the G allele of the polymorphism rs28357094) is associated with reduced muscle strength and above all, ambulation is lost at a younger age in patients with DMD, and appears to be a modulator of glucocorticoid treatment response (55, 56). Other reports have found that variants of the LTBP4 gene influence at what age ambulation is lost in DMD (56, 57). However, these findings require further confirmation in larger genetic studies (58).

CLINICAL MANIFESTATIONS OF DMD

Duchenne muscular dystrophy, is first noticed in boys commonly at the ages of 2 and 5 years, when parents most often notice a delay in "motor milestones and defining symptoms such as difficulty in getting up, frequent falling, toe-walking, gait problems, and flat-footedness" (59). About 50% of the affected boys cannot walk independently at 18 months (59).

The natural course of the disease is fairly predictable, although severity varies between patients, depending on the causative mutation (8). Clinical examination generally reveals calf enlargement (**pseudohypertrophy**), lumbar lordosis, which disappears on sitting, and weakness of the neck flexors. Most DMD patients never learn to jump with both feet together. Weakness of the hip and knee extensors causes the typical **Gower's manoeuvre**: in an effort to stand up from lying on his back, the child needs to turn onto his front and push himself erect by moving his hands up his thighs. Muscle weakness is progressive, starting with proximal weakness of the lower limbs, moving onto the distal lower and then upper limbs, ultimately leading to wheelchair dependence (1, 60). **Loss of independent ambulation**, as defined in DMD occurs by the age of 9 to 12 years, in intermediate-type muscular dystrophy (IMD) between age 13 and 16 years and in BMD, beyond the age of 16 years, though corticosteroid use has made this data less fixed (59). Muscle weakness leads to **scoliosis** in 90% of the cases, with ultimate loss of sitting balance, exacerbated by formation of asymmetric **contractures** of the Achilles tendons and hips. In untreated patients, cardiac and respiratory problems are the cause of death at the mean age of 19 years (59). BMD has a later onset with a more varied presentation and progression, in some cases showing only mild myalgia and muscle cramps with no weakness (61).

Cardiac involvement is seen in all D/BMD patients but generally remains subclinical in the early stages. It is likely that the late presentation of cardiac symptoms is due to the decrease in physical activity, relative to the progressive general muscle weakness. The spread of fibrosis caused by repetitive strain results in left ventricular dysfunction and eventual dilated cardiomyopathy, if left untreated (62). Cardiomyopathy is seen as the determinant of survival in BMD patients, with an incidence of approximately 72%. Research has found that 20% of DMD, and 50% of BMD patients die from cardiomyopathy (60, 63).

For the most part, **respiratory function** in D/BMD patients is normal before loss of ambulation. As a rule, early loss of ambulation predicts early need for ventilation support and respiratory failure. The respiratory function parameter in D/BMD patients is the Forced Expiratory Volume in one second (FEV1) and forced vital capacity (FVC), which peaks shortly before loss of independent ambulation and progressively drops thereafter, with eventual respiratory failure manifesting as lowered energy levels, generalised malaise, weight loss, headaches, sleep disturbance, nocturnal and subsequent daytime hypercapnia. The concurrent increase in the frequency of respiratory infections raises the risk of death from respiratory failure during an infection (59, 64).

Non-progressive **cognitive impairment** in DMD can reach a maximal range of severe intellectual disability (ID) (65, 66). Investigators consistently report the full scale intelligence quotient (FSIQ) in DMD patients as slightly below the population mean, with FSIQ scores of under 70 points seen in 19–35% of DMD cases, and moderate to

severe ID (FISQ<50) noted in 3% of DMD patients (65, 67-69). The gross anatomical structure of DMD-affected brains appears normal (22), although other researchers found slight cerebral atrophy in 66% of DMD cases, the extent of atrophy correlating directly with low intelligence quotient (IQ)(70). There was a relationship between FSIQ results and the location of the DMD mutations and correlate with cognitive deficits and cumulative loss of dystrophin isoforms expressed in the central nervous (CNS) (65). Intellectual disability in BMD patients is reported infrequently, and there is speculation that since cognitive disabilities in D/BMD can precede the onset of muscle weakness and some cases, X-chromosome-linked mental retardation tends to be seen with mutations in the DMD gene (22).

Dystrophin is also seen **in the retina** and some patients with DMD show impaired scotopic and photopic responses obtained by full-field electroretinogram (ERG) (71). Their visual function does not appear to be seriously compromised, although a degree of non-progressive, red-green colour-blindness has been documented (72).

Long **bone fractures** and fractures of the vertebrae are common in D/BMD, because of low bone mineral density, possibly caused by relative immobility, further exacerbated by the long-term use of corticosteroids. Progressive loss of mobility along with steroid treatment can also lead to excessive **weight gain**, which in turn leads to early immobility. On the other hand, loss of appetite frequently accompanying respiratory failure, results in **weight loss**. **Constipation** is a frequent complaint in older boys, due to the involvement of smooth muscle. In later stages, **difficulty in swallowing** and frequent aspiration creates further nutritional and even respiratory complications. D/BMD patients can also potentially presents with "a fatal ''malignant hyperthermia-like reaction associated with rhabdomyolysis, hyperkalaemia and myoglobinuria" (60), when subjected to suxamethonium or a halogenated inhaled anaesthetic (60, 73). This **rhabdomyolytic risk** is a major consideration in their anaesthetic management, and easy access to monitoring aids and intensive care facilities is strongly indicated (60).

D/BMD along with other muscle disorders ranging in presentation from muscle cramps and myoglobinuria, to DMD-associated dilated cardiomyopathy or X-linked dilated cardiomyopathy (XLDCM), are also referred to as **dystrophinopathies,** since all are caused by production of defective or insufficient levels of dystrophin (74, 75).

Diagnosis and Genetic Testing for DMD and BMD

The DMD CARE Consideration Working group in the United States in a recent publication in the Lancet, supported by the Centres for Disease Control and Prevention, formed a policy on methods used in the diagnosis of and Management of D/BMD (59, 76). According to the clinical care recommendations, as set out by the group; DMD diagnosis should be considered irrespective of a positive or negative family history, based upon **abnormal muscle function** in a boy, elevated **serum creatine kinase (CK)** levels (in DMD massively elevated by 10 – 100 x normal, since birth), a result of muscle tissue break down, and including **elevated transaminases** (76).
Clinical Suspicion is then confirmed by:

- **Genetic testing:** Mutation detection provides conclusive evidence and diagnosis. However, it is worth noting that false negative results are a possibility and negative results should be interpreted cautiously as they do not exclude D/BMD diagnosis. A good understanding of the test limitations is therefore required. Testing the mother's carrier status is not strictly part of the

diagnosis but facilitates genetic counseling of the family (77).

- **Muscle biopsy:** Immunohistochemical staining for dystrophin in muscle tissue will reveal absent or reduced dystrophin levels, which can be used to confirm a diagnosis of D/BMD. In most centres however, because of the invasive nature of the procedure, biopsies are taken only if molecular testing is uninformative (59). This is the policy for the service at Red Cross War Memorial Children's Hospital. With current techniques, however, efficiency of mutation detection approaches 100% (78, 79), which allows accurate evaluation of female carriers in a family:

1. Multiplex PCR, Southern blotting and FISH are utilised and able to detect two thirds of mutations in DMD, which are mostly deletions (9, 80).
2. Duplications are detected by utilising quantitative PCR and Southern blotting analysis, which account for 6–10% mutations in males with DMD.
3. Multiple ligation probe amplification (MLPA) is utilised to analyse genes in Carriers and probands, looking at deletions as well as duplications (9).
4. Splicing mutations, single base changes, small deletions make up around a third of DMD mutations. Sequence analysis or mutation scanning is utilised to delineate these changes in the gene.
5. Denaturing gradient gel electrophoresis (DGGE)-based whole-gene mutation scanning and (SCAIP) single-condition amplification internal primer sequencing, are most recent methods of gene testing, and are utilised to detect the remaining third of mutations not yet elucidated by the above tests (81).
6. Muscle biopsy-based approaches utilising direct cDNA sequencing in combination with protein- and RNA-based analyses increase the mutation detection frequency to almost 100%(9, 31).
7. Chorionic villus biopsy or amniocentesis is available as a test for prenatal diagnosis by direct testing for abnormalities in the dystrophin gene (9).

RECENT ADVANCES ON TREATMENT AND CARE OF DMD

In the last few years, the natural untreated course of this condition has improved with interventions (e.g. corticosteroids, cardiac, respiratory, orthopaedic, rehabilitative etc.), quality of life has improved and affected patients may now reach their fourth decade (a significant advance on the previous life expectancy of 14 to 19 years. Research into DMD has continued to accelerate, with a number of different treatment strategies being proposed.

Table 1 Key Standards of care for DMD

Organ System	Intervention
Muscular	Regular specialist health assessments, physiotherapy, glucocorticoids, orthoses, wheelchair, hoist, electric bed, prevention of malignant hyperthermia
Respiratory	Immunisations, treatment of respiratory tract infections, lung function monitoring, pulse oximetry study, cough assistance device, non-invasive ventilation, tracheostomy
Cardiovascular	Cardiovascular assessments with ECHO, ECG, blood pressure measurements, treatment of cardiomyopathy with ACE inhibitors and β-blockers
Gastrointestinal Tract	Monitoring diet, teeth, swallowing, bowel function and weight gain, acid reducers, videofluoroscopy, gastrostomy
Skeletal	Bone density tests (DXA), calcium, vitamin D, bisphosphonates, surgery for scoliosis and joint contractures
Renal/urogenital	Prevention and treatment of dehydration, myoglobinuria and enuresis, urinalyses
Nervous System	Speech and language assessment, pain and sleep control, learning and psychosocial support, cataract screening

DXA, dual-energy x-ray absorptiometry; ECHO, echocardiography.

The role of corticosteroids has become clearer. Glucocorticoids can slow down the decrease muscle function and strength in DMD patients and remain the one medication currently available for such use; this defers loss of ambulation, leads to a reduction in scoliosis and consequently stabilises and improves respiratory function (59, 82). Low-dose steroids are very useful when boys are still walking, to improve motor function. The time of commencement of steroids remains controversial; currently, recommendations are to wait until identifying a plateau in the child's motor development, where motor skills no longer progress and stagnate (59). Once that plateau is identified, steroids are commenced; they are not approved for children still developing motor skills, especially under 2 years (59, 83). Typically, an affected male will progress with motor skills until 4–6 years old. Presently, steroid therapy is the preferred treatment for affected patients of the age bracket 5 to 15 years (59, 83, 84). Some studies, however, suggest that the ideal window for treatment could be less than 5 years (85, 86), where possible our practice is to continue corticosteroid beyond loss of ambulation to promote cardiac protection. Restrictions to this practice have been

excessive weight gain, patient preference and side effects from the corticosteroids. These patients need close monitoring, adjusting dose and timing to avoid unwanted side effects, especially weight gain.
It has been established that prednisone is effective in achieving delay in disease progression, prolongation of ability to walk, maintenance of strength and function, delay in, or prevention of, development of scoliosis, and preservation of respiratory function by limiting fibrosis of the diaphragm (57, 59, 82). The precise mechanism by which prednisone exerts a therapeutic effect is unknown, but it is hypothesised that it is via a stabilising effect on muscle membranes. Prednisone is immunosuppressive, and also has direct effects on muscle cells. It increases the formation of muscle tissue (myogenesis) and inhibits natural cell death (apoptosis). Muscle strength increase is noticeable within 10 days on a steroid dose of 0.75 mg/kg per day, and this benefit can be maintained for 2 years (83). The recommended schedule is daily steroid dosing, although other regimens have been used, including 10 days on, 10 days off, alternate daily doses or weekly high doses (5–10 mg/kg per week (59, 82). Side effects include weight gain, Cushingoid features, hypertension, osteoporosis, hyperglycaemia, easy bruising, fat embolism with trauma and usually transient behavioural problems. The side effects can preclude its ongoing use, although dose reductions, alternative dosing regimens or nocte dosing may overcome these problems. Prednisolone or prednisone can be used. Another steroid that is as effective as prednisolone in maintaining muscle strength and function is deflazacort (87), a methyloxazoline derivative of prednisone. Deflazacort (DFZ) also enhances cardiac and pulmonary function and attenuates the development of scoliosis, including when ambulation is lost. DFZ may cause less severe adverse side effects (e.g. less weight gain) than prednisone (87, 88). DFZ is not freely available, but some neuromuscular specialists use it on individual basis.

A number of therapeutic approaches are being developed for DMD, but most of these are still at the experimental stage in animal models.

Table 1 Experimental treatments for DMD

Table 2: Experimental treatments for Duchenne Muscular dystrophy	
Method	
Cell membrane repair	Exon Skipping
Gene repair	Gene transfer
Muscle or Stem cell therapy	Myostatin inhibition
Stop Codon read through	Utrophin upregulation

Gene therapy trials using new-generation adenovirus carriers known as ‘stealth’ or ‘gutted’ vectors (containing no original viral genes) are being developed to overcome the obstacle of the immune system. Work proceeds on alternative strategies to replace the defective dystrophin gene in DMD patients (89). These include ‘exon skipping’, where synthetic RNA is used to restore the genetic code to produce partially

functioning dystrophin, thereby converting DMD into BMD; and 'utrophin upregulation', which attempts to increase muscle cell production of 'utrophin', a protein related to dystrophin, which can substitute or compensate for it if made in sufficient amounts.
Primitive stem cells in bone marrow have been shown to migrate into muscle and become new muscle cells (63, 90). However, this is still in experimental stages (63, 91). Gentamicin has been found to permit myocytes to ignore an abnormal stop codon in the dystrophin gene and to proceed and synthesise the protein in the 15% of DMD patients who have premature stop codons as their underlying mutation (63, 92). PTC124 is a new agent, traded as Ataluren that may permit ribosomal read through of nonsense mutations. Morpholino antisense oligonucleotides permit exon skipping.
The care of DMD is multidisciplinary involving a plethora of specialists: orthopedic, cardiac, pulmonology, physiotherapists, dieticians, occupational therapists, psychologists, and family and parent/patient support groups.

- **Physiotherapy**: passive or active exercise as well as appropriate orthotic devices to prevent and treat contractures, scoliosis and for walking and/or sitting postural support (seating / wheelchairs).

- **Splinting**: as appropriate, depending of the degree of ambulation and ankle dorsiflection.

- **Surgery**: possible elongation of Achilles tendons and correction of scoliosis.

- **Anaesthesia:** careful preoperative assessment of cardiac and respiratory function and consideration of the rhabdomyolytic risk.

- **Respiratory management**: prophylaxis, prompt diagnosis and treatment of lung infections, positive pressure ventilation to treat hypercapnia and respiratory failure.

- **Cardiovascular management:** regular monitoring of cardiac function (echocardiogram and ECG), treatment with ACE (angiotensin converting enzyme) inhibitors. Additional agents after onset of symptoms.

- **Bone health Monitoring:** diet supplementation using vitamin D and calcium, intravenous bisphosphonates for vertebral fractures, early mobilization post long bone fracture, to prevent early loss of ambulation.

- **Nutrition:** weight monitoring and diet adjustments, use of mild laxatives to relieve constipation, intubation or percutaneous endoscopic gastrostomy (PEG).

- **Addressing learning and emotional difficulties:** occupational and speech therapy, consultation with psychologists and support groups. Planning for appropriate school placement and in-school support.

- **Access to adaptive technologies** i.e. electric beds / ripple mattresses and wheel chairs, computers etc., to aid an independent and functional life (59, 76).

These current care guidelines, especially corticosteroids use, cardiac interventions, and noninvasive ventilation, are all associated better outcomes and quality of life but have

no effect on modifying ongoing disease progression (76, 88, 93)

INTERNATIONAL PERSPECTIVE ON RARE DISEASE REGISTRIES- TREAT-NMD

The different types of variations so far described for the DMD gene range from "large deletions, duplications, point mutations, as well as small rearrangements"(2, 94).

Currently, genetic testing in laboratories is typically done with lack of coordinated integrated information-based registries and this places a substantial burden on genetic service delivery. Postulated treatment strategies are geared towards alleviating the defective gene mutation (92, 95). Finding which type of varaiation is linked to a specific DMD phenotype is central to genetic diagnosis and the formation of a meaningful research ensuring standard clinical care. Over 7,000 (7,149 as of November 2013) mutations are currently in the global database called TREAT-NMD DMD (2). Locus-specific databases (LSDBs) are important for clinical and phenotypic information (2) since they collect, organize, store and analyse all genetic variants of disease. The LSDBs known for DMD are the Leiden muscular dystrophy pages in the Netherlands (27), and the UMD-DMD in France (8).

Despite the fact that formation of these databases has lead to the increased awareness around disease registries and serves as an essential tool for improving quality patient outcomes, yet the number of established national disease registries are still few (96-98). No one country has high enough numbers of patients to embark on translational research (99). Major setbacks to recruitment into clinical trials are the lack of harmonization and the prevailing fragmentation in the neuromuscular community with diverse geographic spread of patients.

Rare diseases, like DMD, are reported to have a low prevalence, however, when considered together, they sum up to very large numbers approaching millions in the United States, European Union and in Australia (13, 99). There is paucity of rare disease prevalence in Africa because of limited resources. Only two national registries exist for DMD in Sudan and Algeria. These registries are both linked to the TREAT-NMD database in Europe (13).
There is an evolving urgency for the formation of rare disease registries worldwide, but in Africa in particular. Such platforms would be critical in integrating data from established rare disease registries and help to form new ones (100)
There is accumulating evidence that advocacy groups motivate much of the need to form rare disease registries (101). Rare Diseases South Africa, a voluntary organization providing advocacy, awareness and support for people affected by rare diseases, and the Muscular Dystrophy Foundation of South Africa, a registered Non Profit Organisation (NPO) whose mission statement is "to support people affected by Muscular Dystrophy and Neuromuscular disorders, and endeavour to improve the quality of life of their members", are examples of such advocacy groups in South Africa. Internationally, a Network of Excellence, funded by the European Union, was launched on the 1st January 2007. This network was named TREAT-NMD and through collaboration has enable experts to come together in the process of creating common standards of care and bring together the neuromuscular community to speed up clinical trials and increase awareness of rare diseases like Duchenne Muscular Dystrophy (13).

THE LOCAL PERSPECTIVE AND RATIONALE FOR THIS STUDY

To follow the efforts of TREAT-NMD through, the dedicated neuromuscular service at Red Cross War Memorial Children's Hospital manages the single largest collection of children with Duchenne Muscular Dystrophy in the country. The hospital, as South Africa's leading centre for post-graduate specialist paediatric medical and surgical training, offers specialised care facilities and high levels of expertise. "The Guidelines for Medical approach to Care of Children with DMD – Guidelines from the Neuromuscular Clinic", authored by Professor Jo Wilmshurst, head of Paediatric Neurology at RXH (and a clinical supervisor in this study), and approved by PANDA SA (Paediatric Neurology and Development Association of Southern Africa) offer a clear guide as to the appropriate and achievable standard of care within the South African context, based on the recommendations set by international bodies (i.e. US Centres for Disease Control and Prevention, DMD Care Considerations Working Group).

The service operates along international lines as a multidisciplinary team with input from ancillary services, pulmonology, cardiology, developmental, orthopaedics, histopathology, genetics and counsellors. With the possibility of treatment becoming available, patients that would qualify for treatment need to be identified. The service has established a database of these children with confirmed DMD, but there is a need to consolidate and expand the information in the database to form a patient registry.

The South African DMD (SADMD) registry is the first local attempt to consolidate clinical and genetic information on South African DMD patients with the potential to be considered for contemporary clinical trials and to be well informed regarding the most recent and up to date standards of care. This cohort will provide the biggest longitudinal data collection of DMD boys in Africa with the possibility to link with centres of excellence like TREAT-NMD.

Aim

This study aim to describe the concept and design of the first DMD disease registry of South Africa using Research Electronic Data Capture (REDCap)

Objectives

The objectives for forming the registry are:

- To update and expand the existing database and to populate it with current information relating to the clinical phenotypes of the patients inclusive of their cardiac, respiratory, cognitive, oromotor / gastroenterological, motor and orthopaedic evolution

- To assess the effect of introduction of corticosteroid and cardiac interventions on the course of these children for their cardiac and pulmonary, duration of ambulation, orthopaedic complications and resultant need for BIPAP support.
- To correlate the clinical profile of this patient group with those who have confirmed genetic mutations and identify those who may be remedial for the latest gene therapy and who would benefit from extended screening to confirm is this is the case.
- To establish if the South African cohort carry a similar range of mutations compared to those listed internationally.
- To see if direct relationship can be identified between specific mutation and clinical course.
- To identify if the range of patients carrying potentially remedial gene therapy mutations is in-line with the incidence reported internationally

8.6 Conclusion

This study describes the concept and design of the first DMD disease registry of South Africa using Research Electronic Data Capture Tool .The accumulated data from this cohort will represents the biggest longitudinal data collection of DMD boys in Africa and could form a reference for research in the Neuromuscular community.

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9) Chapter 2
9.1 Publication Ready Manuscript

Development of a Duchenne Muscular Dystrophy registry for children in South Africa to optimize care.

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***Targeted Journal**: South African Medical Journal (SAMJ)*

9.2 Abstract

Background
The most prevalent, most lethal of the inherited dystrophies is Duchenne Muscular Dystrophy (DMD) and globally, the incidence is reported to be 1 in 3500 live male births. Currently, DMD has no cure, the latest care guidelines, especially on corticosteroids, cardiac interventions, and non-invasive ventilation, are all associated with improved muscle function, survival and quality of life. This reflects the fact that the natural history of DMD has been changed by these effective measures. Despite these advances, the progression and disastrous outcome of the disease cannot be modified and DMD remains life limiting. Potential therapeutic approaches that target the causative genetic variations raise hopes of promising treatment for DMD. Many clinical trials of molecular genetic therapies have been planned and conducted for DMD. In South Africa, even though mutational characteristics of South African DMD/BMD patients have been described in several studies, the development of experimental therapies faces many challenges due to the lack of epidemiological data, the natural history of the disease and information about clinical care amongst Africans. Understanding the disease course of the local population can lead to better care approaches, further with the possibility of gene therapy becoming available, patients that would qualify for such treatment need to be identified. Hence the need for a DMD specific disease registry.
Objective: This study aim to describe the concept and design of the first DMD disease registry of South Africa using Research Electronic Data Capture (REDCap)

Methods: The registry was developed using REDCap's web based online designer accessed through the Clinical Research Centre (CRC) in the Faculty of Health Sciences at the University of Cape Town, and the workflow methodology was adopted to manage the registry. Clinical data from DMD patients form the database and consists of seven parts: 1) Enrolment details, 2) Background data, 3) Current disease, 4) Schooling, career prospects, and life style/psychological details, 5) Basic activity of living scale, 6) power Chart, 7) Current motor function/symptoms. Electronic case report forms were created from these clinical data by the use of REDCap and for specific variables serial entries were possible relating to disease progression. We adopted international data standards proposed by TREAT-NMD, a global network of registries on DMD to ensure our data is internationalised and comparable to other registries.

Results: Retrospective data entry combined with dynamic prospective recording of data was utilized in this project. Building on an existing database, 100 confirmed DMD boys are currently eligible for inclusion into the registry.
The registry database consist of 7 forms collecting information on clinical and genetic information, which is subdivided into 100 items making a total of 210 variables. As our registry is an on-going study, sequential analysis of accumulated data will done going forward to review trends on our DMD patients.

Conclusions: This work described the concept and design of our DMD registry and the meticulous steps followed to its establishment with REDCap, the focus is to consolidate clinical and genetic information on South African DMD patients that will translate to clinical research and form the basis for these patient information to be linked internationally. It is the hope that such an effort can be replicated in the conceptualisation of new disease registries.

9.3 Introduction/Background

The most prevalent, most lethal of the inherited dystrophies is Duchenne Muscular Dystrophy (DMD) and globally, the incidence is reported to be 1 in 3500 live male births (1-4)

Variation of the dystrophin gene is what leads to Duchenne, Becker and a third intermediate form of muscle disorder, collectively known as the dystrophinopathies (1). Muscle fibre degeneration is the primary pathologic process; leading to weakness as the principal symptom.

The different types of variations so far described for the DMD gene range from "large deletions, duplications, point mutations, as well as small rearrangements"(2, 5).

The current care guidelines, especially on corticosteroids use, cardiac interventions, and non-invasive ventilation, are all associated with better outcomes and quality of life but have no effect on modifying on-going disease progression (6-8). Postulated treatment strategies are geared towards alleviating the defective gene mutation (9,10). Finding which type of mutation is linked to a specific DMD phenotype is central to genetic diagnosis and the formation of a meaningful research ensuring standard clinical care. Over 7,000 (7,149 as of November 2013) mutations are currently in the global database called TREAT-NMD (2). Despite the fact that formation of these databases has lead to the increased awareness around disease registries and serves as an essential tool for improving quality patient outcomes, yet the number of established national disease registries are still few today (11-13). No one country has sufficient patients to embark on translational research (14). Major setbacks to recruitment into clinical trials are the lack of harmonization and the prevailing fragmentation in the neuromuscular community with diverse geographic spread of patients (15).

Rare diseases, like DMD, are reported to have a low prevalence, however, when considered together, they sum up to very large numbers approaching millions in the United States, European Union and in Australia (3,14). There is paucity of rare disease prevalence in Africa because of limited resources and only two national registries exists for DMD in Sudan and Algeria. These registries are now both linked to TREAT- NMD database in Europe (3).

There is an evolving urgency for the formation of rare disease registries world wide, but in Africa in particular. Such platforms would be critical in integrating data from established rare disease registries and help form new ones (16)

There is accumulating evidence that advocacy groups motivate much of the need to form rare disease registries (17). Rare Diseases South Africa, a voluntary organization providing advocacy, awareness and support for people affected by rare diseases, and the Muscular Dystrophy Foundation of South Africa, a registered Non Profit organisation (NPO) whose mission statement is "to support people affected by Muscular Dystrophy and Neuromuscular disorders and endeavour to improve the quality of life of their members", are examples of such advocacy groups in South Africa. Internationally, a Network of Excellence, funded by the European Union, was launched on the 1st January 2007. This network was named TREAT-NMD and has enabled experts to create common standards of care and bring together the neuromuscular community to speed up clinical trials and increase awareness of rare diseases like Duchenne Muscular Dystrophy (3).

Locally in South Africa, the dedicated neuromuscular service at "Red Cross War Memorial Children's Hospital" manages the single largest collection of children with Duchenne Muscular Dystrophy in the country. The hospital, as a "leading South

African centre for post-graduate specialist paediatric medical and surgical training", offers specialised care facilities and high levels of expertise.

The service operates along international lines as a multidisciplinary team with input from ancillary services, pulmonology, cardiology, developmental, orthopaedics, histopathology, genetics and counsellors. With the possibility of treatment becoming available, patients that would qualify for treatment need to be identified. The service has established a database of these children with confirmed DMD, but there is a need to consolidate the information in the database to form a patient registry.

The South African DMD (SADMD) registry is the first local attempt to consolidate clinical and genetic information on South African DMD patients with the potential to be considered for contemporary clinical trials and be well informed regarding the most recent and up to date standards of care. This cohort will provide the biggest longitudinal data collection of DMD boys in Africa with the possibility to link with centres of excellence like TREAT-NMD.

Aim

This study aim to describe the concept and design of the first DMD disease registry of South Africa using Research Electronic Data Capture (REDCap)

Objectives

The objectives for forming the registry are:

- To update and expand the existing database and to populate it with current information relating to the clinical phenotypes of the patients inclusive of their cardiac, respiratory, cognitive, oromotor / gastroenterological, motor and orthopaedic evolution
- To assess the effect of introduction of corticosteroid and cardiac interventions on the course of these children for their cardiac and pulmonary, duration of ambulation, orthopaedic complications and resultant need for BIPAP support.
- To correlate the clinical profile of this patient group with those who have confirmed genetic mutations and identify those who may be remedial for the latest gene therapy and who would benefit from extended screening to confirm is this is the case.
- To establish if the South African cohort carry a similar range of mutations compared to those listed internationally.
- To see if direct relationship can be identified between specific mutation and clinical course.
- To identify if the range of patients carrying potentially remedial gene therapy mutations is in-line with the incidence reported internationally

9.4 METHODS

REDCap Application

"REDCap electronic data capture tool is hosted and managed by the University of Cape Town's eResearch Centre and the UCT Clinical Research Centre. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources."

Vanderbilt University developed the REDCap application but it is available free of charge to institutional partners that satisfied the basic criteria for a web server that supports, secure sockets layers (SSL), PHP, MySQL database connections (18,19). UCT satisfied all these criteria and has become a REDCap consortium member.

DMD Patients

All patients with confirmed DMD diagnosis (or pending diagnosis) according to DNA confirmation or compatible confirmation on muscle biopsy or with a confirmed affected relative where there is compatible X-linked inheritance are eligible for inclusion. Currently, only children managed through the Red Cross War Memorial Children's Hospital neuromuscular service will be included, as these patients receive standardised and consistent care protocols which are not routine in other SA centres with less capacity, at this stage. Collaboration with the genetics service research team was undertaken exploring the known genetic mutations of these patients in relation to their clinical profile and their potential to undergo further screening for gene therapy.

Exclusion criteria for this database are patients referred with a presumed diagnosis of DMD/BMD who subsequently were found to have other pathologies. Similarly patients suspected to have DMD/BMD but who lacked the definitive diagnostic closure via DNA analysis or muscle biopsy or family history, were also excluded. In isolated cases patients with known DMD were excluded where there was insufficient information documented or they were lost to follow-up.
The protocol for this study, the patient information and authorization (Appendix 2) and relevant supporting information were all submitted, reviewed and approved by the "Hospital Research Committee and the University of Cape Town Human Research Ethics Committee".
For every patient and carer, appropriate patient/caregiver assent/consent will be obtained according to South African regulations. As the study is non-invasive and collating existing data, telephonic consent could be taken initially and formally signed at the caregiver's convenience when they attend the clinic. This is to ensure that all data is current by the time the current actual therapeutic interventions are available that the viable patients are already identified. There will be a clear explanation to the patient/caregiver in his or her own language, supplemented with a patient/ care giver information sheet (Appendix 2) which will be given to the patient/ caregiver to read and consider prior to enrolment.
Patients and caregivers will be invited to give permission for the clinical data to be registered on the RCWMCH DMD database. If they choose for their personal and

medical data to be uploaded in the database, it will be stored in accordance with the data protection act and pseudonymised. Encrypted data will then be saved in the database.

Patients and their caregivers participate voluntarily in this study with the option not to participate or withdraw consent for their data to be stored on the registry/database at any time without prejudice. Patients and caregivers will be reminded that they may remove the data from the register on a yearly bases, when they are contacted to update their record.

Registry description

With assistance from the technical team of the Clinical Research Centre (CRC) in the Faculty of Health Sciences at the University of Cape Town, the database was developed using REDCap's web based online designer. This database consists of seven parts: 1) Enrolment details, 2) Background data, 3) Current disease, looking at serially recorded information on BMI, respiratory involvement, chest physiotherapy treatment, corticosteroid use, scoliosis, bone health and nutritional management, 4) Schooling, career prospects, and life style/psychological details, 5) Basic activity of living scale, 6) power chart, 7) current motor function/symptoms.

The enrolment and background data forms are developed to capture mandatory set of data including age at presentation, first symptoms at presentation, demographics, family history, referral route, and initial creatinine kinase values. This mandatory section is crucial for a meaningful data collection going forward so that each patient will have a minimum amount of information recorded. The rest of the items focus on DMD defined clinical manifestations and such data are collected in other sections of the registry listed above, repeated annually, and as appropriate. Self reported Activities of Daily Living (ADL) is to capture patient's reported QOL on an annual basis to encourage active participation.

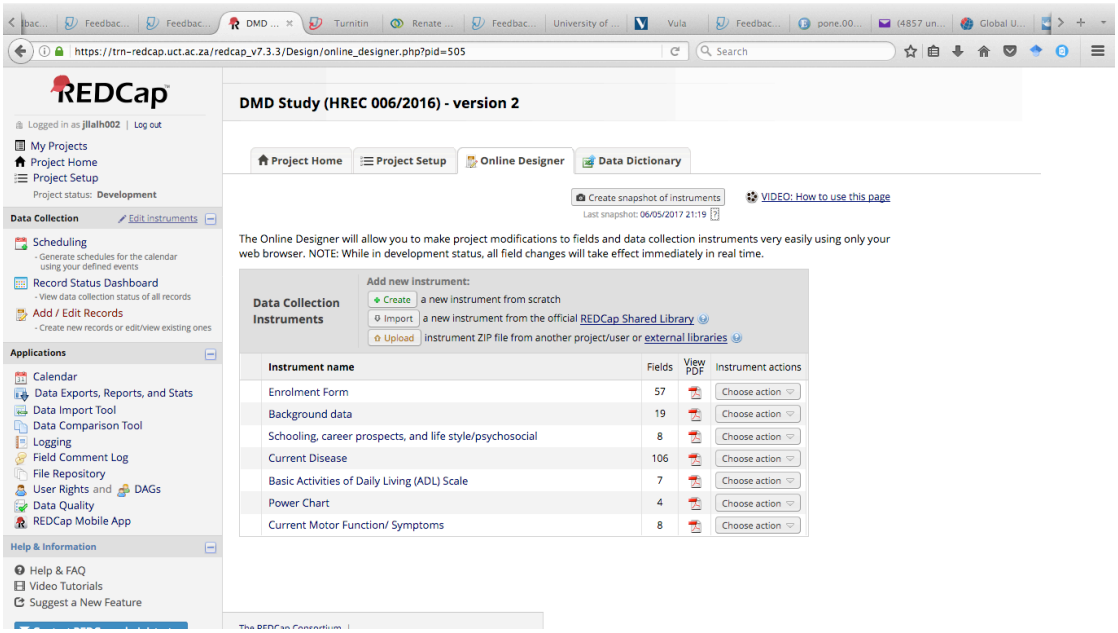

Figure 1 Screen shot of data forms as shown on REDCap

The registry operates on a longitudinal module and utilises the repeating events feature of REDCap, which allows one to repeat an entire event of instruments together in unison. This is useful for several instruments whose data correlates together. The repeating events feature allows one to create only one single event that can be repeated in an unlimited fashion.

Hospital clinical records and clinic visits records are our main sources of data, prospectively and retrospectively on an annual basis starting from the first documented visit to the Neuromuscular Service of RCWMCH, this will continue as a dynamic data collection.

Statisticians and Information technology (IT) specialists reviewed the database design and planning process and provided detailed advice on the methodology and data items.

Following a key recommendation of TREAT-NMD on creating registries for rare diseases, the SADMD system is developed with the aim to become an open-source software solution. The REDCap framework was chosen as it allows rapid prototyping and its flexibility makes it easy to customise the application such as adding additional fields or options. It provides a very powerful and easy to use ORM (Object-relational mapping) to build Complex SQL database queries. Its template engine allows the development of user-friendly interfaces, with HTML/CSS and Javascript. It is also very well integrated with the Apache Web server for deployment in production environments.
As with most authentication-based systems, the SA National Duchenne Muscular Dystrophy Registry in the future can be most broadly broken into two sections: the component available to unauthenticated users and the part available to authenticated users.
Only one page of the DMD Registry will be available to unauthenticated users: a landing page explaining the aims of the registry and linking to the government and non-profit stakeholders within the project.
Authenticated users of smaller scale neuromuscular centres will be provided access

associated with a particular working group, with patient data access being restricted solely to patient registered by that working group in that centre.
Authenticated users of smaller scale neuromuscular centres will be provided access associated with a particular working group, with patient data access being restricted solely to patient registered by that working group in that centre.

Creating the Registry database

The REDCap was used to create and run the DMD registry, "it is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources (20); 5) as well as a built-in project calendar, a scheduling module, ad hoc reporting tools, and advanced features, such as branching logic, file uploading, calculated fields and possibility of creating surveys for quick feedbacks"(19-21).

The REDCap server provides training videos and teaching resources on REDCap to guide users, a formal training or prior experience is not required to use the application.

Nonetheless, the main administrator for REDCap at UCT was consulted to assist with project programming, and guide on data quality and security and to agree with the standard operating procedures. The implementation stage included: I) UCT network access to REDCap by logging with staff/ student credentials, II) Clicking on to the "Create New Project" icon to create and designed the project III) Defining variables and their properties to enable you to create data collection instruments, IV) Dataset preview and testing in anticipation for statistical output and analyses, v) Providing rights and permission to users, VI) Switching Project to production mode for real data collection.

Data entry and Quality

Data entry errors are a possibility and test runs are important to try to curtail errors as much as possible. REDCap data quality module allows for execution of data quality rules upon project data to check for discrepancies in data, this feature was utilised in this project and predefined rules filtered errors and discrepancies. These predefined rules were important since our project constitutes many fields and records. Data validation was possible as a REDCap feature by limiting data sets and set ranges for numerical data fields, the data quality module reports any values out of range, incorrect data type and outliers.

The main investigator pioneered the data extraction and input, with review, adjustments and additions by the supervisor.

The supervisor ensured that standard operating procedures were adhered to strictly, especially data entry and collection. Statisticians will be were consulted on a 6 monthly basis for quick checks. The allowance for entry mistakes is 5 per 100, otherwise all clinical data entry is questioned and a full scale review undertaken and reassessed.

Database Management

This project is primarily managed by the neuromuscular service of the RCWMCH, headed by the Project administrator, Professor Jo Wilmshurst who oversees the entire functioning of the project including personnel associated with data entries. The team work closely with statisticians and IT specialists of the University of Cape Town's eResearch Centre and the UCT Clinical Research Centre who advised on the database structure and design. The main investigator developed the electronic data collection forms and the IT specialists and statisticians review them. The neuromuscular service team recruited and attained consent/assent from subjects for the study if they met eligibility criteria. This relationship is shown in Figure 1

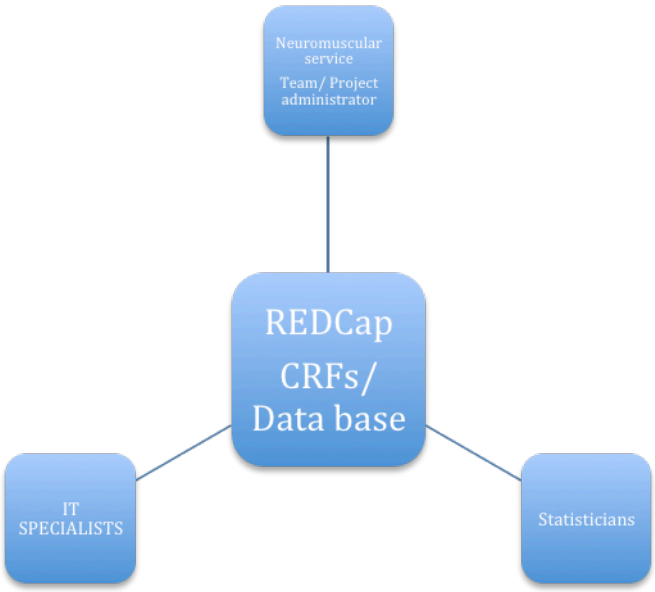

Figure 2 Team players in managing the DMD Registry

9.5 Results

Retrospective data entry combined with dynamic prospective recording of data was utilized in this project. Building and expanding on an existing database, 100 confirmed DMD boys are currently eligible for inclusion into the registry.

Structure of the registry

The registry database consist of 7 forms collecting information on enrolment, background details, current disease, schooling/ career prospect, activities of daily living, power chart, current motor function/symptoms, which is subdivided into 100 items making a total of 210 variables as shown in Table 1

Table 2 DMD registry structure, NIV, noninvasive ventilation, BMI, body mass index, CPK, creatinine phosphokinase

Enrolment details	Study ID, Consent/Assent done, Date subject signed consent, Currently included in a clinical trial/study, Trial/study name, Name of person doing the entry, name, date of birth, age, gender, address, next of kin, ethnicity, race, primary condition, diagnosis code, presumed clinical subtype, date diagnosed, age at diagnosis, muscle biopsy details, genetic details, gene therapy eligibility
Background information	Age at first symptoms, type of symptoms presented with, hospital admissions and reason for admission, best motor function, wheel chair use, age of starting wheel chair use, type of wheel chair, source of wheel chair, type of wheel chair, age of complete loss of ambulation, family history of DMD, CPK test details, referral details of patient
Current Disease on annual basis	Weight, height, BMI, respiratory involvement and respiratory co-morbidity, NIV, form of NIV, indication for NIV, type of NIV, form taken, tracheostomy details, special investigations, lung function details, chest infection episodes, result of polysomnography, need for pulmonology referral and reasons for doing so, chest physiotherapy details, steroid use, date steroid started and reason for starting, current steroid dose and regimen, side effects so far. Scoliosis and cardiac involvement, Bone health, physical therapy interventions, nutritional management
Schooling/career prospects	School curriculum, life style, and psychosocial issues like education on DMD, emotional issues, social support, and support grant, type of support grant.
Basic activities of dialing living	Bathing, dressing, toileting, transferring, continence, feeding
Power Chart	MRC average score (x5), Gower's time score, 10 metre

	run
Current motor function/symptoms	Able to walk, able to run, able to climb stairs, arm involvement, participates in sports, myalgia, time myalgia is experienced

Clinical data standards

This registry has been set-up on the background of clinical and translational research readiness in mind. In this regard, we have collected dataset that is concise and guided by pertinent aspects of required inclusion criteria for clinical research known as mandatory dataset. The variables and items described above are all based on standardised elements proposed by TREAT-NMD data standards (3), the defined data set allows a coordinated approach to clinical trial readiness and our records to be comparable and anonymously aggregated.

In addition to the mandatory dataset, we have collected additional data, such as items relating to daily activities of living of our patients and the natural history of the disease, to look at other variables of interest to the neuromuscular service here at RCWMCH. All necessary approvals are in place

Data Storage

Displayed below is a screen short (Figure 3) showing part of current responses and records with their status for every event and data collection instrument. Clicking on a button opens a new tab/window in the browser to view that record on that particular data collection instrument. We provide form-level user privileges to restricted certain data collection instruments, so that users can only be able to view those instruments, and if they if they are provided with user rights Data Access Group (DAG), making them able to view records assigned to that user group.
This also shows the enrolment visit (Visit 0), and annual visits. On enrolment, all instruments are administered or completed for baseline minimum data on all patient, on annual visit, the enrolment form and background data are not repeated, but the rest of the instruments are repeated to be able to look at trends. This task is possible by utilizing the repeat instrument functionality of REDCap.

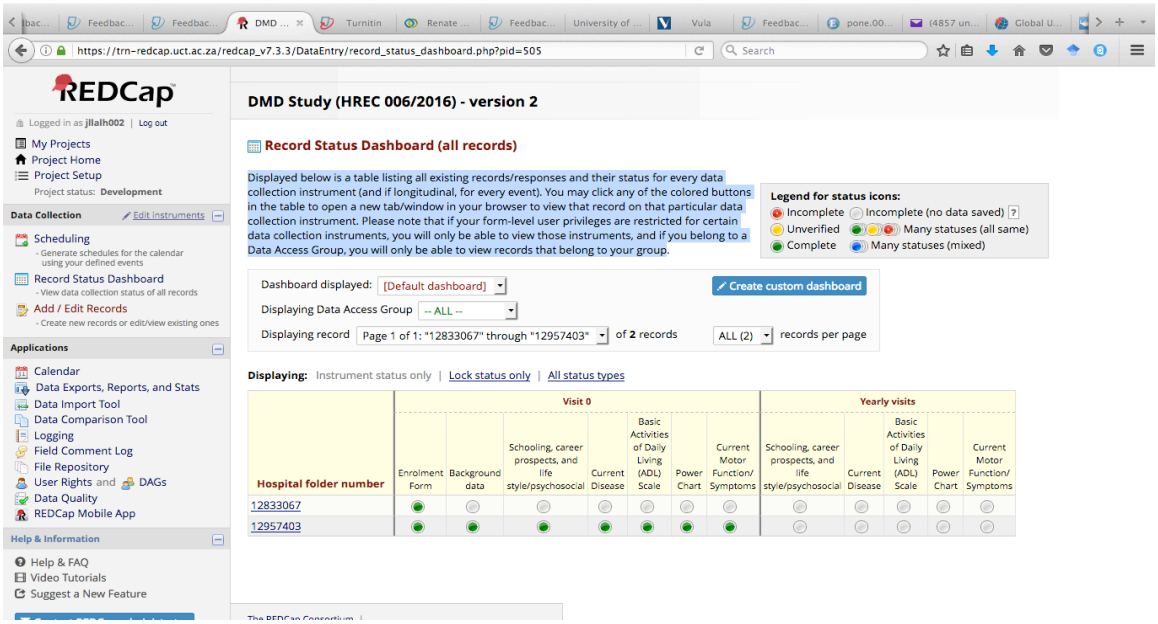

Figure 3 Screen shot of part of the DMD registry, status dashboard

Security of Data

Users are granted access to this project and user privileges of those users are managed by the project administrator, this provides complete patient confidentiality since all information are encrypted in the Redcap server. Roles are created to which users are assigned (optional). User roles are useful when there are several users with the same privileges. Roles and rights can be given for access many tasks ranging from managing participants, file repository, logging, data export, data import, data entry rights, project design, calendar, to data quality. Logging is required for every encounter with the data, an audit tract. The registry administrator has, in addition, the privilege to lock the data after all finalisation checks. UCT unique user names and passwords are required for researchers to access the database. Figure 4

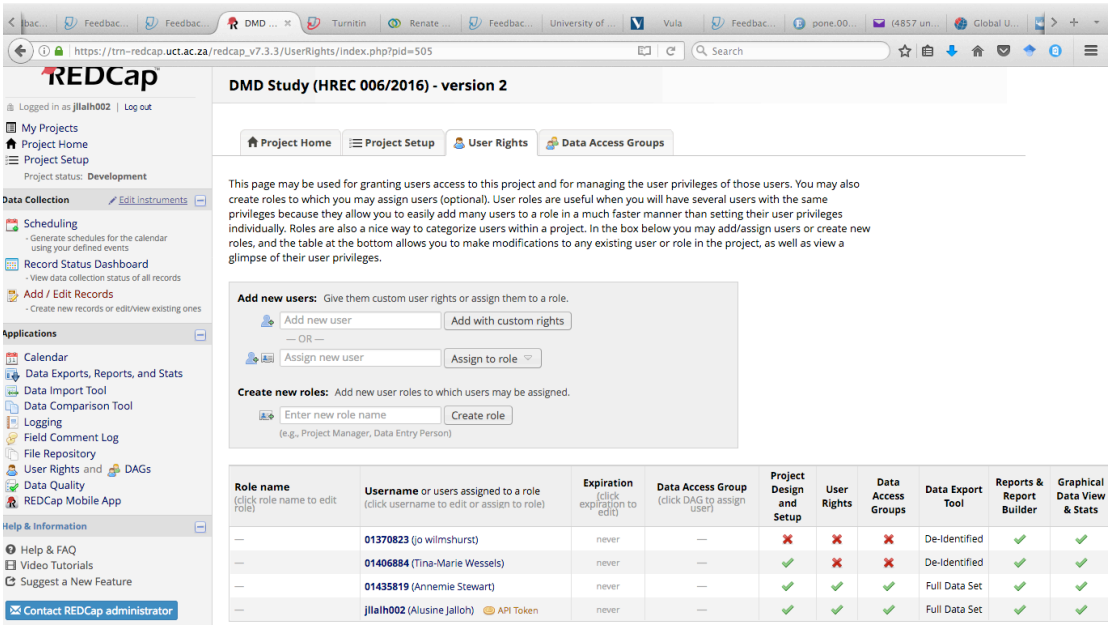

Figure 4 Granting User rights and permissions

REDCap true Strength in data collection to support Research

Our database was designed to collect mandatory baseline data on all subjects, followed by annual updates of data collection by combining retrospective data collection with ongoing prospective entry of data records.
The project brought forward a host of advantages to using the REDCap application for registry design and pointed out few challenges encountered in the design of the electronic case report forms (eCRF).
The ease of form construction was noted to be a major advantage. Forms were created by a point and click interface on the web; data dictionaries externally created in excel can be uploaded. Moreover, the University of Cape Town's eResearch Centre and the UCT Clinical Research Centre technical team allowed quick answer to questions regarding technical difficulties in the design particularly on the use piping and branching logic etc.
Equally important on using the REDCap application was the clear and easy way of creating customised reports and exporting the data. Multiple data formats can be exported for use in various statistical soft wares.
Rapid quality assessment, associated with the software, made it possible to identify data errors, which were corrected by the neuromuscular team on a continuing basis.
Data elements and entry forms are specific; this was an advantage in avoiding errors on entering records.
However, challenges and limitations were identified in the creation of this registry using the REDCap application. This was illustrated at the time piloting of data began, entry form problems were noted, this warranted the REDCap main administrator to archive the old entry forms, temporarily take down the database, fixe the errors, and re-start the database. Therefore, meticulously reviewing of the data instruments prior to and testing and retesting them rigorously and imaginatively before going into production are encouraged.
Nonetheless, these limitations and challenges are not major when compared to the rest of the advantages stipulated above. This registry demonstrates that the REDCap is indeed an effective tool in collecting research and clinical data.

9.6 Discussion

This Duchenne Muscular Dystrophy registry is built on the foundation of need to consolidate clinical and genetic information on South African DMD patients. Clinical and translational research is needed and should be based on the most recent and up to date standards of care. In this manuscript, we describe the concept and design of our DMD registry. We adopted a diversity of steps including: meticulous database planning, the use of REDCap to construct the electronic case reports forms, as well as adopting clinical data standards.

This study method is also an attempt to follow through international efforts in data consolidation through a reproducible research protocol, making it possible for replication to other medical registries. To conform to this, we adopted international data standards proposed by TREAT-NMD, a global network of registries on DMD, funded by the European Union. This allows for internationalisation of our registry, accordingly we followed the defined standard items recommended by TREAT-NMD (3, 16), as well as data elements from other international designs such as rare disease HUB (100, 105). Electronic information in health systems is now recognised and accepted in the international community making it crucial to adopt established data standards. Consequently, this means a more versatile registry and the possibility of our registry being able to collaborate with other institutions like TREAT-NMD.

Successful workflow models aligned to the daily and clinical practice with minimal interruption has produced successful registries (12, 16, 19, 23), in our work, we have made an effort to align the clinical services of the neuromuscular unit to consenting and asking patients and care givers to allow for their information to be uploaded.

Our data collection primarily focuses on, background information, diagnosis, interventions, genetic data, which are all essential to identifying subjects eligible for clinical and translational research.

As our registry is an on-going study, sequential analysis of accumulated data will done going forward to review trends on our DMD patients, as a result this will aim to provide evidence-based decisions for DMD patients in our setting. The registry data will be used to assess the effect of introduction of corticosteroids and cardiac interventions on the course of these children for their cardiac and pulmonary, duration of ambulation, orthopaedic complications and resultant need for BIPAP support. Also to correlate with the clinical profile of this patient group with those who have confirmed genetic mutations and identify those who may be remedial for the latest gene therapy and who would benefit from extended screening to confirm if this is the case. To establish if the South African cohort carry a similar range of mutations compared to those listed internationally. Lastly to see if direct relationships can be identified between specific mutations and clinical course, as well as to identify if the range of patients carrying potentially remedial gene therapy mutations is in-line with the incidence reported internationally.

9.7 Conclusion

This work describes the concept and design of a DMD registry and the detailed steps followed for its establishment with REDCap. The focus is to consolidate clinical and genetic information on South African DMD patients that will translate to clinical research and to form the basis for these patients' information to be linked internationally. It is the hope that such an effort can be replicated in the conceptualisation of new disease registries.

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11) Appendices

Appendix 1: Data capturing instruments

Confidential

Enrolment Form

Hospital folder number _____

Consent

Consent/Assent done ◯ Yes ◯ No

Date subject signed consent _____
(if [icf_signed] = '1')

Name of person doing the entry
◯ Alusine
◯ Jo
◯ Wendy
◯ Isatu
◯ other

Contact Information - Participant

First Name _____

Middle name _____

Last Name _____

Street _____
(if [icf_signed] = '1')

City _____
(if [icf_signed] = '1')

Province (South Africa only)
◯ Western Cape
◯ Eastern Cape
◯ Northern Cape
◯ KZN
◯ Free State
◯ Gauteng
◯ North West
◯ Mpumalanga
◯ Limpopo

Postal code _____

Phone number (own, 1) _____
(Include Area Code, if [icf_signed] = '1')

Phone number (own, 2) _____
(Include Area Code, if [icf_signed] = '1')

Contact Information - Alternative contact person

Contact person
_____
(if [icf_signed] = '1')

Contact telephone
_____
(Include Area Code, if [icf_signed] = '1')

Relationship to participant
_____
(if [icf_signed] = '1')

E-mail
_____
(if [icf_signed] = '1')

Demographic characteristics

Date of birth
_____

Age today (years)
_____

Race
◯ Black African
◯ White
◯ Coloured
◯ Asian
◯ Other

Specify race
_____

Home language
◯ Afrikaans
◯ English
◯ Ndebele
◯ Northern Sotho
◯ Sotho
◯ Swazi
◯ Tsonga
◯ Tswana
◯ Venda
◯ Xhosa
◯ Zulu
◯ Other

Specify home language
_____

Sex
◯ Female ◯ Male ◯ inderminate
◯ other

Known allergy
◯ No known allergies ◯ allergic
◯ not specified

specify Allergy
_____

Primary condition

Primary condition	◯ Muscular Dystrophy ◯ Other ((reason being enrolled))
Diagnosis code	_____ (ICD10-CM)
Presumed clinical subtype	◯ Duchenne muscular Dystrophy (DMD) ◯ Intermediate muscular Dystrophy (IMD) ◯ Becker muscular Dystrophy (BMD) ◯ Female carrier ◯ Unknown
Diagnosis text (1)	_____ (free text - only if necessary!)
Date diagnosed	_____
Age at diagnosis	_____
Diagnosed by doctor...	_____ (Surname, initials, state if not specified)
Diagnosed at... (Western Cape facility)	_____
... or other facility	_____
Diagnosis notes (e.g. contact details for referring doctor)	_____ (state if not specified)

Confirmation of diagnosis

Diagnosis confirmed	◯ Yes ◯ No
Diagnosis investigated further by:	☐ Muscle biopsy ☐ Genetics ☐ From relative
Muscle biopsy confirmed the dystrophy?	◯ Yes ◯ No
DNA number	_____
If Genetics, which tests done:	_____
Genetic confirmation?	◯ Yes ◯ No
Deletion: all exons tested	◯ Yes ◯ No ◯ not specified
Exonic deletion	_____
Duplication: all exons tested	◯ Yes ◯ No ◯ not specified
Exonic duplication	_____
Deletion/Duplication Boundaries Known	◯ Yes ◯ No

Small/Point Mutations	_____ (DNA Change Sequencecs)
Open Reading Frame	◯ disrupted ◯ maintained
Translational Effect	◯ central rod domain repeat 13 ◯ Dp427m-unique N-terminus ◯ Transcription factor binding site ◯ central rod domain repeat 12 ◯ Actin-binding domain and central rod domain ending mid-repeat 13 ◯ Central rod domain repeat 22 ◯ Actin-binding domain ◯ Central rod domain repeats 6-11 ◯ Central rod domain hinge 4
Affected Isoforms	_____
Impact at the Junction	_____
Targeted mutation testing in the patient but testing of all exons in a relative male patient	◯ Yes ◯ No ◯ Unknown
Gene Therapy Eligibility	◯ Yes ◯ No
Gene Therapy Eligibility: type	◯ Read through ◯ Exon skipping ◯ Other
other gene therapy, please specify	_____ (please specify)
Final Diagnosis	◯ Duchenne Muscular Dystrophy (DMD) ◯ Becker Muscular Dystrophy (BMD) ◯ Intermediate Muscular Dystrophy (IMD) ◯ Female Carrier ◯ Unknown

Background data

Hospital folder number	_____
Age at first symptoms	_____
First symptoms were	☐ Delayed walking ☐ Frequent falls ☐ Difficulty with running or climbing stairs ☐ Others, Please specify.....
Admitted to hospital	◯ Yes ◯ No
Reason for admission	◯ Yes ◯ No
Number of hospitalisations	_____
Best Motor Function (including participation in sports, ability on stairs, walking distance, etc.)	◯ Can currently Walk ◯ Walks with support, struggles to get up ◯ Cannot currently Walk ◯ Other
Best Motor Function (specify)	_____
Wheelchair use?	◯ Yes ◯ No
Age of starting wheelchair use	_____
Time spent on wheelchair	◯ Part time ◯ Full time
Type of wheelchair	◯ Manual ◯ Powered
source of Wheel chair	_____
Age of complete loss of ambulation	_____
Family History of DMD?	◯ positive ◯ negative ◯ relative with high CPK
CPK test done?	◯ Yes ◯ No (Creatinine Phosphokinase)
CPK date?	_____
CPK value	_____ (U/L)
Was this patient referred?	◯ Yes ◯ No
If yes above, from where?	◯ private hospital ◯ Tertiary level practice in public ◯ secondary level hospital ◯ community health centre ◯ others

Current Disease

Hospital folder number _____

Annaul Review

Date _____

Weight _____ (kilograms)

Height _____ (cm)

BMI _____

Respiratory

Respiratory Involvement ◯ Yes ◯ No

Respiratory co-morbidity and complications
☐ OSA
☐ Hypoventilation
☐ Aspiration
☐ GORD
☐ Recurrent RTIs
☐ Loss of Ambulaton
☐ Cardimyopathy
☐ Pulmonary hypertension
☐ Bronchectsis
☐ Atelectasis
☐ Kyphoscoliosis

Non-invasive Ventilation ◯ Yes ◯ No

Form of Non-invasive ventilation
◯ Nocturnal ventilation
◯ Daytime ventilation

Indication for nocturnal ventilation
◯ signs and symptoms of hypoventilation(FVC< 30%)
◯ Baseline SpO2 < 95% and/or blood or end-tidal CO2 >45mmHg while awake
◯ An apnoea-hypopnoea index>10 per hour on polysomnography ◯ other

indication for day time ventilation
◯ Self extension of nocturnal ventilation into waking hours
◯ Abnormal deglutition due to dyspnoea, which is relieved by ventilatory assistance
◯ inability to speak a full sentence without breathlessness.and/or
◯ symptoms of hypoventilation with baseline SpO2< 95% and/or blood or end-tidal CO2 >45mmHg while awake

Non- invasive ventilation type
◯ BiPAP
◯ CPAP
◯ not specified

Form Taken	◯ Via Tracheostomy ◯ Via Mask
indication for tracheostomy	◯ Patient and clinician preference ◯ patient cannot successfully use non-invasive ventilation ◯ inability of local medical infrastructure to support non-invasive ventilation ◯ Failure to achieve extubation during critical illness despite optimum use of NIV and mechanically assisted cough ◯ other
Special Investigation	◯ Overnight oximetry ◯ Full polysomnography ◯ Videoflouroscopy(MBS) ◯ BA swallow/Milk scan ◯ Other
Lung function done	◯ Yes ◯ No
Lung function date	_____
FVC	_____
FEV1	_____
FEV1/FVC ratio	_____
BTS criteria met	◯ Yes ◯ No
Peak Cough flow	_____
chest infection	◯ Yes ◯ No
Number of chest infections	_____
CO2 level	_____
HCO3	_____
Result Of Polysomnography	_____
Indications of Sleep study(polysomnography)	☐ Vital capacity less than 40% predicted ☐ Loss of ambulation ☐ Infants with significant weakness ☐ Symptoms of OSA or hypoventilation ☐ Diagphragmatic weakness ☐ Rigid spine syndrome
Needing pulmonology referral	◯ Yes ◯ No
Reason for referral to pulmonology	☐ Needing sleep study ☐ Greater than 2 singnifican respiratory infections in 6 months ☐ Complications e.g. atelectasis, bronchiectasis ☐ ICU admission for severe respiratory infection/illness ☐ Significant scoliosis or prescoliosis surgery

Chest physiotherapy treatment

Reciving physiotherapy	◯ Yes ◯ No
Assisted cough: Inspiratory assistance	☐ Breath stacking ☐ Glossopharygeal breathing ☐ Manual insufflation ☐ Mechanical insufflation
Assisted cough: Expiratory assistance	☐ Manual assisted cough ☐ Mechanical Assisted cough
Secretion mobilisation Technique	_____
Spinal care and Seating	_____
Others (Excercise, muscle training, etc.)	_____

Steroids

On steroids	◯ Yes ◯ No
Date steroids first prescribed	_____
Age steroid was started	_____
Reason for starting steroid	_____
Current steroid dose	◯ 0.5mg/kg/day ◯ 0.75mg/kg/day ◯ 1 mg/kg/day ◯ other
steriod regimen	◯ daily ◯ alternate days ◯ 10 days on, 10 days off
Steroid stopped	◯ Yes ◯ No
Reason for stopping steroids	◯ Complete loss of ambulation ◯ Steroid side effects ◯ other
List chronic side effects so far, if any	◯ Hypertension ◯ Obesity ◯ Delayed puberty ◯ Behavioral problems ◯ Short stature ◯ other

Scoliosis

Scoliosis present	◯ Yes ◯ No
Age first noted	_____
Degree of scoliosis curve/Cobb's angle	0 180 360 (Place a mark on the scale above)
Scoliosis curve direction	◯ Right ◯ Left
Scoliosis surgery	◯ Yes ◯ No
Scoliosis surgery date	_____
Type of surgery	_____

Cardiac

Cardiac involvement	◯ Yes ◯ No
Clinically symptomatic	◯ Yes ◯ No
Current cardiac problem(s)	☐ Not further specified ☐ Arrhythmia/conduction block ☐ Cardiomyopathy ☐ Others, please specify
Other cardiac problems (specify)	_____
On cardiac medication	◯ Yes ◯ No
Which cardiac medication(s)	☐ ACE inhibitors ☐ Calcium channel blockers ☐ Beta blocks ☐ Others, specify.....
Which other cardiac medication(s)	_____
Date ACE inhibitor was started	_____
Which ACE inhibitor	◯ Enalapil ◯ captopril ◯ others
Current Dosage	_____
Dosage adjustment	◯ Yes ◯ No
Reason for Dosage Adjustment	_____
New drug dosage	_____
change to a new drug	◯ Yes ◯ No

Reason for changing to a new drug _____

New drug _____

ECHO done ◯ Yes ◯ No

Indication for ECHO
◯ Baseline check
◯ follow up check
◯ Cardiac Symptoms
◯ Abnormal ECG

ECHO date _____

Left ventricular ejection fraction
0 50 100
(Place a mark on the scale above)

Fractional Shorting
0 50 100
(Place a mark on the scale above)

LVID
35 56
(Place a mark on the scale above)

LVIS
20 40
(Place a mark on the scale above)

Relevant summary from ECHO
◯ systolic dysfuction ◯ diastolic dysfunction ◯ posterior wall dysfunction
◯ anterior wall dysfunction
◯ LV Dilatation ◯ Globally moderate to severely impaired function
◯ Globally mild to moderately impaired systolic function ◯ poor thickening with hypo kinetic walls ◯ Structurally normal heart ◯ other.....
(if more than one, choose most severe description)

ECG Done
◯ Yes
◯ No

ECG summary
☐ Normal
☐ sinus tachycardia
☐ shortening of PR interval
☐ occurence of Deep Qwaves in lead 1,aVL and left precordial leads
☐ IRBBB
☐ CRBBB
☐ IRBBB PLUS CRBBB
☐ LBBB
☐ broad R waves in V1-V6
(Please provide fields to be captured for ECG)

Overall ECG summary _____

Bone health

Poor bone Health	◯ Yes ◯ No
Complications from poor bone Health	☐ Fractures ☐ Osteopaenia ☐ Osteoporosis ☐ Khyphoscoliosis ☐ Bone pain ☐ Reduced quality of life ☐ Unclear
Impact of Fracture	◯ non-ambulant ◯ worsening pain ◯ other
fracture management	◯ Internal fixation ◯ splinting or casting ◯ not specified
Bone densiometry done	◯ Yes ◯ No
Date bone densiometry was done	_____
Age at bone densiometry	_____
Indication for Bone densiometry/radigraph	☐ Khyphosis noted on clinical examination ☐ Back pain is present, to assess vertebral compression fractures ☐ Not listed
BMD	_____
BMD Z score	_____
Body region	◯ Spine ◯ Whole body
BMD classification	◯ Within expected range for chronological age ◯ Below expected range for chronological age
Interventions for poor bone health	☐ Vitamin D ☐ Calcium ☐ Bisphosphonates ☐ None
Indiacation for Vitamin D	◯ Treatment for proven deficiency ◯ Supplementation, levels cannot be maintained ◯ Supplementation, levels not tested
Vitamin D levels	_____

Physical Therapy Interventions

Orthoses	◯ Yes ◯ No
Type of Orthoses	◯ Ankle foot orthoses(AFO) ◯ Knee-ankle-foot orthoses(KAFO) ◯ Resting hand splints

standing device use	◯ Yes ◯ No
Standing devices	◯ passive standing ◯ power standing wheelchair
lower limb contractors	◯ Yes ◯ No
surgical intervention for lower limb contractors	◯ Yes ◯ No

Nutritional Management

Needing referral to an expert dietician/nutritionist	◯ Yes ◯ No
reason for referral to dietician/nutritionist	◯ At diagnosis ◯ at initiation of glucocorticoids ◯ Underweight ◯ Risk of becoming overweight(85-95th age percentile) ◯ Overweight(>95th age percentile) ◯ unintentional weight loss or gain ◯ Major surgery planned ◯ Chronically constipated ◯ Dysphagia ◯ Other
Needing intervention from speech and language therapist	◯ Yes ◯ No
Reason for referral to speech and language therapist	_____ (list indications)
gastric tube placement	◯ Yes ◯ No
Gatrotomy tube	◯ PEG ◯ Open surgery
indication for gastrotomy tube placement	_____ (list indication)

Basic Activities of Daily Living (ADL) Scale

Hospital folder number	_____
Date	_____
1. Bathing (sponge bath, tub bath or shower) - Receives either no assistance or assistance in bathing only one part of the body.	◯ Yes ◯ No (Independent)
2. Dressing - Gets clothes and dresses without any assistance except for tying shoes.	◯ Yes ◯ No (Independent)
3. Toileting - Goes to toilet room, uses toilet, arranges clothes, and returns without any assistance (may use cane or walker for support and may use bedpan/urinal at night.)	◯ Yes ◯ No (Independent)
4. Transferring - Moves in and out of bed and chair without assistance (may use cane or walker).	◯ Yes ◯ No (Independent)
5. Continence - Controls bowel and bladder completely by self (without occasional "accidents").	◯ Yes ◯ No (Independent)
6. Feeding - Feeds self without assistance (except for help with cutting meat or buttering bread).	◯ Yes ◯ No (Independent)

Katz S., Down, TD, Cash, HR, et al. (1970) progress in the development of the index of ADL. Gerontologist 10:20-30.

Current Motor Function/ Symptoms

Hospital folder number	_____
Date	_____
Able to walk	◯ Yes ◯ No
Able to run?	◯ Yes ◯ No
Able to climb stairs	◯ Yes ◯ No
Arm involvement?	◯ Yes ◯ No
Participate in Sports	◯ Yes ◯ No
Myalgia	◯ Yes ◯ No
when is myalgia experienced	◯ End of a busy day ◯ At night ◯ On awakening ◯ others

Schooling, career prospects, and life style/psychosocial

Hospital folder number _____

School
- ◯ Normal school
- ◯ Special unit in regular school
- ◯ Special school
- ◯ Not at school

Life style
- ◯ Pursuing courses at tertiary education
- ◯ Working with computers
- ◯ Others.....specify

Life style (specify) _____

Psychosocial

Education on DMD
- ☐ Parent
- ☐ Patient
- ☐ None
- ☐ Clarification of information from other sources
- ☐ Regular feedback to ensure no misunderstanding
- ☐ Other family members are very much involved

Emotional issues
- ☐ Preparatory explanation to parents of probable feeling (guilt,anger,depression)
- ☐ Explanation regarding any misapprehension or strange beliefs about nature of illness

Social Support
- ☐ Social workers
- ☐ Muscle Dystrophy Association
- ☐ None

Support grant ◯ Yes ◯ No

Type of support grant _____

Power Chart

Hospital folder number _____

Date _____

MRC average score (x5), all muscle groups _____

Gowers time score _____
(seconds)

10 metre run _____

Appendix 2: Consent/assent forms and participants information sheets

University of Cape Town

SCHOOL OF CHILD AND ADOLESCENT HEALTH

DIVISION: PAEDIATRIC MEDICINE

RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL

KLIPFONTAIN ROAD, RONDENBOSCH,7700

TEL:+2721658111

Informed consent for:

DUCHENNE MUSCULAR DYSTROHY DATABASE STUDY
HREC 006/2016

Title: Clinical and Genetic Phenotypes of children with Duchenne Muscular Dystrophy in the Western Cape of South Africa

A Descriptive Retrospective Observation Cohort Study

This informed consent is for parents and legal guidians of children with Duchenne Muscular Dystrophy seen at the Red Cross War Memorial Children's Hospital(RXH) neuromuscular service

Name of Princinpal Investigator: Professor Jo Wilmshurst

Name of Student Reseacher: Dr. Alhaji Alusine Jalloh

Name of Organisation : Red Cross War Memorial Children's Hospital

Email: alhajialusine@yahoo.com

Contact: 0730070257

This informed consent form has three parts:

- **Information sheet(to share information about the research with you)**
- **Consent form for patient**
- **Assent form for children 7-13 years old**

Information For Patients

We ask your permission for your child's medical information to be entered into a confidential research database. The following information explains why the research is being done and what it will involve. Please read the following information and if there is anything that is not clear, or if you have any further questions, please ask us (our contact details are printed above and on page 3).

You are being invited to take part in this research database because your child has a rare neuromuscular disease called DUCHENNE MUSCULAR DYSTROPHY. The aim of this research is to establish a database, which will be computer record containing information about your child's medical condition. This database of patients with your child's condition will be used to understand whether the care we are giving is in-line with other centres overseas, to identfy children who may be responsive for possible gene therapy and to understand if our children are responding to our current maangement in-line with other centres. The database will convert information which is already recorded in the medical records into an electronic resourse.

The main coordinator of this database set up is Professor Jo Wilmshurst, the head of Neurology at Red Cross War Memorial Children's Hospital, Email: jo.wilmshurst@uct.ac.za.

Please read this information and if you agree for your child's information to be entered into the registry we will ask you to sign a consent form gving permisison for this to occur. If you have any questions please contact us before signing the consent form.

How will I benefit from my child's data being entered into this registry?

This database aims to benefit patients living with Duchene muscular dystrophy. You will be contacted if we are able to offer new treatments for your child's condition. Whilst this care would happen as part of the routine clinic, the database will help to identify these children with more efficency and rapidity.

You will not receive any payment or any other financial benefit as a result of giving permission for your child's medical information being entered into the database.

Will information about me be kept confidential?

All information we record about your child, will be treated confidentially. We make every effort to ensure your child's data is kept safe. Details of your child's specific diagnosis as well as personal information (name, age, address, gender) will be stored on the database. Only members of the team given specific permission will be allowed to look at this information. If we publish any research or other documents based on

information from the database, this will not identify your child by name.

Do I have to join the database and can I withdraw if I change my mind?

Joining the database is voluntary. Should you wish to withdraw your child's information from the database you will be free to do so at any time without having to provide any explanation. If you wish to withdraw, you should get in touch with the staff in charge of the database. Contact details are provided below. Joining or leaving the database will in no way affect the care for your child's condition.

How will my data be used?

The main aim of us asking you to be part of the registry is to help to understand the disease course in our patients in South Africa and ideally to see if we can identify children who may be responsive to new treatments.

How will my details be updated?

Your child's details will be updated on the database annually, based on the clinical information recorded from the routine clinic visits. You can contact us at any time if you need to amend your child's details. You are free to have your child's information withdrawn from the database at any time.

Who is funding the research?

This research is self funded, however, applications for funding will be sent to the Muscular Dystrophy Foundation and the University of Cape Town Masters of Medicine Fund

Who has reviewed this project?

All research conducted within the University of Cape Town has to be reviewed by an ethics committee to make sure we are not doing anything harmful to your child or your child's data in this project.

Details of ethics committee:

Reference number:

What if I have any concerns?

If you have any concerns or other questions about this study or the way it has been carried out, you should contact:

1) The principal investigator: **Professor Jo Wilmshurst , the head of**

Neurology at Red Cross War Memorial Children's Hospital, Email: jo.wilmshurst@uct.ac.za.

2) Main study investigator: **Dr. Alhaji Alusine Jalloh, Cell Phone: 0730070257**

Thank you for taking the time to read this information sheet

CONSENT FORM FOR PATIENT

DUCHENNE MUSCULAR DYSTROPHY DATABASE STUDY

Please place a TICK ☑ in the Box for a YES and a CROSS ☒ for a NO

1	I confirm that I have read and understand the information sheet dated 25th September, 2015, Version number 2 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3	By signing this document, I understand that I give consent for the storage of data on my child in the DUCHENNE MUSCULAR DYSTROPHY DATABASE.	
4	I understand that the data I provide may be used to inform and plan future research.	
5	I understand that the results from future research may not have any direct implications for my child or my family.	
8	I confirm I am happy for relevant information about my condition to be added to database entry on my behalf.	
9	I am happy to consent for my child to be included in this DATABASE	

Please sign here:

……

Name of parent / guardian:

…… ……

Date

…… …… ……

Name of person taking consent Date Signature

ASSENT FOR CHILDREN 7-13 years old

Study title: Clinical and Genetic Phenotypes of children with Duchenne Muscular Dystrophy in the Western Cape of South Africa

A Descriptive Observational Cohort Study

Principal Investigator: Professor Jo Wilmshurst

Main Investigator: Dr. Alhaji Alusine Jalloh

Why you are here?

You come to this clinic because you have a medical problem which stops your muscles from working properly.The doctors would like to put together all the information recorded in your medical records into an electronic database for you and other children with the same muscle problem. If there is anything in this form that you do not understand, please ask your parent, your guardian or the study staff.

Why are they doing this study?

The doctors want to set up a computer based summary of your medical information. , This information will be used to understand if we are looking after you in the same way as children in other countries, to see if there are other treatments we should be offering to you and to see if your muscle problem is behaving differently to children in other countries with the same problem.

What will happen to you?

If you want to be in the study these things will happen:

- You will be asked to give permission for your medical information to be put into a computer based summary (a "registry"). This information will be confidential meaning that only the doctors putting the information in will know that it is you information.
- All information about your medical condition will be taken from your hospital medical records and you will not have to do anything additional beyond your usual visits to the hospital.

Will the study hurt?

- No – the study is collecting information and does not require you to do anything extra.

Will you get better if you are in the study?

This study will not make you feel better or get well. The doctors may find something that will help other children like you later. Also they may be able to find new treatments which you would be more likely to respond to, but this is in the future.

What if you have any questions?
You can ask questions any time, now or later. You can talk to the doctors, your family or someone else.
The main coordinator of this database set up is Professor Jo Wilmshurst, the head of Neurology at Red Cross War Memorial Children's Hospital,
Email:jo.wilmshurst@uct.ac.za

Telephone: 021 6585370

Who will know what I did in the study?
Any information you give to the study staff will be kept private (*or secret*). Your name will not be on any study paper and no one but the study staff and your family will know that it was you who was in the study.

Do you have to be in the study?
You do not have to be in the study.

It is completely alright to say if you do not want to be in this study. Your parents will also be told about the study and asked if they would like you to be part of it. Even if your parents want you to be in the study you can still say no. The doctor will still take care of your *Medical Condition*.

Even if you say yes now you can change your mind later.

Assent

I want to take part in this study. I know I can change my mind at any time.

_____ **Verbal assent given Yes ☐**

Print name of child
[If verbal assent obtained the process must be clearly documented in the research or medical file]

Written assent if the child chooses to sign the assent.

_____	_____	_____
Signature of Child	**Age**	**Date**

[The following statement and signature is required]:

I confirm that I have explained the study to the participant to the extent compatible with the participants understanding, and that the participant has agreed to be in the study.

_____	_____	
Printed name of Person obtaining assent	**Signature of Person obtaining assent**	**Date**

Appendix 3: MMed Candidature Approval

Vuyi Mgoqi

From: Vuyi Mgoqi
Sent: 18 August 2016 04:31 PM
To: 'alhajialusine@yahoo.com'
Cc: Jo Wilmshurst
Subject: Jalloh: Confirmation of Approval of Study Proposal

Dear Dr Jalloh

Candidature Approval (JLLALH002)

Degree	MMed in Paediatrics and Child Health
Title	Clinical and genetic phenotypes of children with Duchene muscular dystrophy in the Western Cape of South Africa – An observational study
Department	Paediatrics and Child Health
Supervisor	Prof J Wilmhurst
Ethics Approval	006/2016

I am pleased to advise that the Chair of the Dissertations/Doctoral & Masters Committee has approved your candidature for the above degree on behalf of the Committee. Formal approval was obtained by publication in the Dean's Circular, PG-Med Jun2016.

Yours sincerely

Vuyi Mgoqi

Vuyiseka Mgoqi |Receptionist: PG Academic Administration |Faculty of Health Sciences | University of Cape Town | Room N2.19, Wernher & Beit North, Health Sciences Campus, Anzio Rd, Observatory, 7925 | ☎ + 27 21 404 7662 🖷 + 27 21 406 6584 | Office Hours: 08h30 - 16h30 Unavailable Hours: 13h00 - 13h30

1

Appendix 4: HREC approval letters with extension

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

28 January 2016

HREC REF: 006/2016

Prof J Wilmshurst
Paediatric Neurology
Paediatrics and Child Health
Red Cross Hospital

Dear Prof Wilmshurst

PROJECT TITLE: CLINICAL AND GENETIC PHENOTYPES OF CHILDREN WITH DUCHENNE MUSCULAR DYSTROPHY IN THE WESTERN CAPE OF SOUTH AFRICA - AN OBSERVATIONAL STUDY (Masters Candidate - Dr A Jalloh)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th January 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Dr Alhaji Alusine Jalloh will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492 • **Facsimile** [021] 406 6411
Email: Sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

19 January 2016

REF NO: R001/2016

Prof J Wilmshurst
Paediatric Neurology
Paediatric & Child Health
Red Cross War Memorial Children's Hospital
Rondebosch

Dear Prof Wilmshurst

PROJECT TITLE: DUCHENNE MUSCULAR DYSTROHY REGISTRY

Thank you for your submission to the Faculty of Health Sciences Human Research Ethics Committee (HREC).

The HREC has **approved** the registration of your registry.

The registration of this registry is valid until 30 January 2019.

Please provide the HREC with an update if the registry continues beyond this period.
Please Note: All research, including that undertaken for a master's or doctoral degree, using registered databases, registries and repositories, requires submission as a new study. It requires an application form (FHS013) and a protocol which has undergone departmental review. The study will receive its own HREC REF number which will be linked to the main database or repository.

Please provide the HREC with an update if the registry continues beyond this period.

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR MARC BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Hrec/ref:R001/2016

UNIVERSITY OF CAPE TOWN

HUMAN RESEARCH ETHICS COMMITTEE
- 4 APR 2017
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.4.2018
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	5/4/17

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	30th March 2017		
HREC REF Number	006/2016	Current Ethics Approval was granted until	30th January 2017
Protocol title	Clinical And Genetic Phenotypes of children with Duchenne Muscular Dystrophy in the Western Cape of South Africa		
Principal Investigator	Professor Jo Wilmshurst		
Department / Office Internal Mail Address	Paediatric Neurology Paediatrics and Child health, Red Cross War Memorial Childrens Hospital		
1.1 Does this protocol receive US Federal funding?		☐ Yes	✓No

2. Protocol status (tick ✓)

✓	Research-related activities are ongoing
☐	Data collection is complete, data analysis only
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.	

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		20
Total number of records or specimens collected, reviewed or stored since last progress report		
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐ Yes	✓ No

4. Signature

Signature of PI		Date	31/03/2017

Appendix 5: Instructions to author of Chosen article(Next page)

Author Guidelines

The *SAMJ* has launched a new submission and tracking system. Authors will be required to register a profile on the Editorial Manager platform in order to submit a manuscript.

To submit a manuscript, please proceed to the *SAMJ* Editorial Manager website:

www.editorialmanager.com/samj

To access and submit an article already in production, please see the guidelines here.

Author Guidelines

Please view the Author Tutorial for guidance on how to submit on Editorial Manager.

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

SAMJ policies

- Types of articles considered by the SAMJ
- Article Processing Charges
- Authorship
- Conflict of interest
- Research ethics committee approval
- Clinical trials
- Protection of patient's rights to privacy
- Copyright notice
- Privacy statement
- Ethnic classification
- CPD

Manuscript preparation

- Preparing an article for anonymous review
- General article format/layout
- Preparation notes by article type
- Illustrations
- Tables
- References

From submission to acceptance

- Submission and peer-review
- Production process
- Changing contact details or authorship

Publication

- Online versus print
- Errata and retractions
- Indexing

SAMJ Policies

Type of articles considered by the SAMJ

The *SAMJ* will no longer limit the articles accepted to those that have 'general medical content', but is intending to capture the spectrum of medical and health sciences, grouped by relevance to the country's burdens of disease. This content will include research in the social sciences and economics that is relevant to the medical issues around our burden of disease. Please see 'A new vision for the *SAMJ* – and a call for papers' for a full discussion of the new directions for the *SAMJ*.

We accept the following types of articles:

- Research
- Reviews
- Clinical trials
- Editorials
- In Practice (Previously Forum incl. Case Reports)
- Correspondence
- Obituaries
- Book reviews
- Ad hoc supplements e.g. guidelines, conference/congress abstracts, Festschrifts*

The following articles are by invitation only:

- Guest editorial
- Continuing Medical Education (CME)

*Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Publication Fees

All articles published in the *South African Medical Journal* are open access and freely available online upon publication. This is made possible by applying a business model to offset the costs of peer review management, copyediting, design and production, by charging a publication fee of R5 000 (ex vat) for each research article published. The charge applies only to **Research** articles submitted after 1 March 2017. The publication fee is standard and does not vary based on length, colour, figures, or other elements.

When submitting a Research article to the *SAMJ*, the submitting author must agree to pay the publication fee should the article be accepted for publication. The publicaiton fee is payable when your manuscript is editorially accepted and before production commences for publication. The submitting author will be notified that payment is due and given details on the available methods of payment. Prompt payment is advised; the article will not enter into production until payment is received. Queries can be directed to claudian@hmpg.co.za.

Please refer to the section on 'Sponsored Supplements' regarding the publication of supplements, where a charge is applicable. Queries can be directed to dianes@hmpg.co.za or claudian@hmpg.co.za

Authorship

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Author contributions should be listed/described in the manuscript.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structuresto ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchershave been adhered to.

Clinical trials

Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The *SAMJ* therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Protection of rights to privacy

Patient

Information that would enable identification of individual patients should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

Any individual who is identifiable in an image must provide written agreement that the image may be used in that context in the *SAMJ*.

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form that outlines Author and Publisher rights and terms of publication. The **Author Agreement form** should be uploaded along with other submissions files and any submission will be considered incomplete without it.

Material submitted for publication in the *SAMJ* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement. The *SAMJ* does not hold itself responsible for statements made by the authors.

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Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note that is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

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SAMJ is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, *SAMJ* also publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn the reader 3 CEUs. Administration of our CPD

programme is managed by Medical Practice Consulting. To complete questionnaires and obtain certificates, please visit MRP Consulting

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).

- Units should be preceded by a space (except for % and °C), e.g. '40 kg' and '20 cm' but '50%' and '19°C'.
- Please be sure to insert proper symbols e.g. μ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out
    - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
    - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
    - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Appendix 6: Copy right and Permissions(Next page)

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May 14, 2017

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Requestor type	Individual
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Portion	Figure/table/extract
Number of figure/table/extracts	2
Descriptionof figure/table/extracts	Fig 1, fig 2 and Fig 3
Will you be translating?	No
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Title of your thesis / dissertation	Development of a Duchenne Muscular D cildren in South Africa to optimise care
Expected completion date	Oct 2017
Estimated size(pages)	60
Requestor Location	Alhai Alusine Jalloh Institute of Child Health University of Cape Town Klipfontain Road, Rondebosch Cape Town, Western cape 7700 South Africa Attn: Alhai Alusine Jalloh
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Appendix 7:

D9 – Approval of Change of Title - 2015

University of Cape Town

Faculty of Health Sciences

Form D9: Approval for Change of Title

Please complete and return to Vuyi Mgoqi (Vuyi.Mgoqi@uct.ac.za) in the Postgraduate Office

Name and student no	Alhaji Alusine Jalloh JLLALH002
Degree name (e.g. MSc(Med) in Physiology)	MMed Paediatrics
UCT Student Email address for correspondence	JLLALH002@myuct.ac.za
Student signature:	
Date:	18th May,2017

Qualifications	MBChB, FCPaeds(SA)
Old Title	Clinical and Genetic phenotypes of Duchenne Muscular Dystrophy in the Western Cape of South Africa
Proposed new title	Development of a Duchenne Muscular Dystrophy Registry in South Africa to Optimise Care
Proposed title change supported by Departmental Research Committee (DRC)	Name of Chair, Department Research Committee: Professor Brenda Morrow Chair Signature: 2017 -05- 10 Department of Paediatrics & Child Health Research Committee

Please give reason for the need for to change your thesis/dissertation title:

The care of children with DMD is complex and multidisciplinary across multiple health domains. At the start of the MMED project it was envisioned that the student would collate a sample of data from a proportion of the children with DMD. But the potential for the research has expanded with the access to the Redcap database system. With this tool the student can develop an exceptionally useful data capturing tool which will enable sequential data capturing across the multiple modalities of the study area.

However the based on the depth of understanding of the condition, encompassed in a literature review, along with the insight into the role of data capturing tools, such as Redcap, this research study would result in significantly more study hours than the previous data sampling would have encurred.

As a result I would like to support the student in motivating for a change in study title as above.

The extent of the research remains unchanged in that the student is still reviewing the literature and creating a registry but the third step of collecting and analysing the data on the patient cohort is significant amount of work, with each branch of sub-conditions carrying their own outputs (e.g. cardiac complications of DMD, bone health in children with DMD, pulmononary function in children with DMD, current care practice and time to loss of ambulation, genetic expression with clinical phenotype, pharmacogenetics – children remedial to intervention in Africa, developmental expression in DMD etc etc). The registry will be created with all these data entry points to allow this data to be sequentially captured from over the last 17 years.

To reflect the extent of this research I would recommend that this stage is registered for a follow-on degree for which the student will complete a further PG degree protocol application form.

(if you require more space than this then please attach a separate page)

I support / do not support the thesis/dissertation title change as requested by this student

Supervisor name and signature:	Name: Jo M Wilmshurst	Signature:	Date:18/05/2017

D9 – Approval of Change of Title - 2015

I recommend / do not recommend the thesis/dissertation title change as requested by this student			
HOD name and signature	Name: A.C. ARGENT.		Date: 19/5/17

For office use:

I approve / do not approve the thesis/dissertation title change as requested by the above student			
Deputy Dean: Postgraduate Affairs:	Name:	Signature:	Date:

Received by:	Name:	Date:	
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